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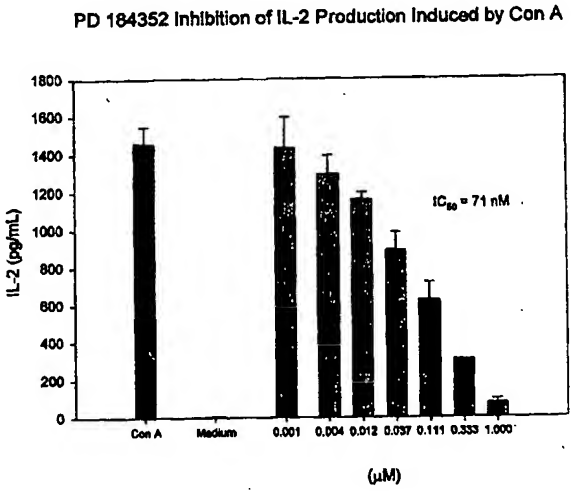
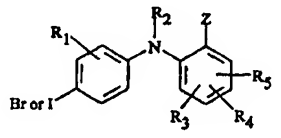
(54) Title: USE OF A MEK INHIBITOR FOR PREVENTING TRANSPLANT REJECTION

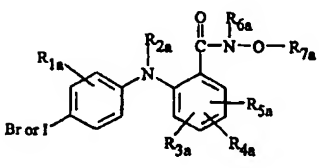
(57) Abstract

This invention provides a method for the prophylaxis or maintenance of rejection of transplants of organs, cells, limbs, and tissues in mammals, comprising administering a selective MEK inhibitor, preferably a compound of formulas (I) and (II).





(I)



(II)

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USE OF A MEK INHIBITOR FOR PREVENTING TRANSPLANT REJECTION

FIELD OF THE INVENTION

This invention relates to a method for preventing mammals that have undergone an organ, tissue, cell, or limb transplant from rejecting the transplant. The method comprises administering an effective amount of a MEK inhibitor, ideally a phenyl amine derivative.

BACKGROUND OF THE INVENTION

Transplantation of organs and limbs has become a common procedure to treat mammals that have diseased organs, or have been the victims of accidents or other traumas that have resulted in loss of organ function or limbs. Routinely transplanted organs include the liver, kidney, pancreas, and lung. Other types of transplantation are also common, such as skin, bone marrow, and small intestine. Limb transplantation includes fingers, toes, and larger limbs such as arms.

Transplant rejection involves both humoral immunity and a cell-mediated immune reaction, or a delayed type hypersensitivity response in a mammal patient. As a result, the patient receives an immunosuppressant agent to control or at least diminish the rejection response. While several immunosuppressants are currently available for clinical use, each is associated with adverse side effects. For example, cyclosporine is a cyclic peptide which inhibits the T-cell production of several cytokines, including IL-2 (interleukin-2), IL-3, IL-4, IL-5, IFN-δ, and probably other lymphokines. Cyclosporine is used extensively for the prophylaxis of organ rejection in allogeneic kidney, liver, and heart transplants. Cyclosporine is often used in combination with other immunosuppressant agents such as corticosteroids or azathioprine. Unfortunate side effects associated with cyclosporine include nephrotoxicity, hepatotoxicity, severe renal dysfunction, tremor, hirsutism, and hypertension.

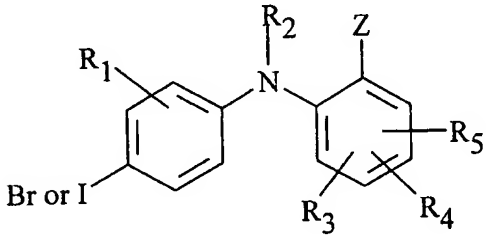
Another immunosuppressive agent is mycophenolate mofetil, the 2-morpholinoethyl ester of mycophenolic acid that is frequently used by patients

receiving allogeneic renal transplants. This agent is often used in combination with other immunosuppressive agents, including cyclosporine and corticosteroids. Like cyclosporine, mycophenolate mofetil can cause side effects, most notably the increased risk of developing lymphomas and other malignancies, particularly concerning the skin. Adverse effects on fetal development have also been noted.

In view of the above, there is a continuing need for immunosuppressant agents not only useful for treating or preventing transplant rejection but also with less severe side effects than those associated with existing therapy. According to the present invention, compounds that are MEK inhibitors are useful for preventing rejection of transplants in mammals. Moreover, these potent immunosuppressive agents may have fewer or no adverse side effects. The compounds to be administered according to this invention are described in US Patent No. 5,525,625, and in WO 98/37881, both of which are incorporated herein by reference.

SUMMARY OF THE INVENTION

This invention provides a method for the prevention of rejection in a mammal of transplanted organs, tissues, and limbs, said method including administering an effective immunosuppressive amount of a selective MEK inhibitor to a subject who has undergone a transplant or is scheduled to undergo a transplant. In a preferred embodiment, the MEK inhibitor administered is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran, also known as "98059", as described in US 5,525,625. In another preferred embodiment, the immunosuppressive agent administered is a phenyl amine compound of Formula I or II:



I

In formula (I), R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN. R_2 is hydrogen. R_3, R_4, and R_5 are independently selected from hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, and -(O or NH)$_m$-$(CH_2)_n$-R_9. R_9 is hydrogen, hydroxy, COOH, or $NR_{10}R_{11}$; n is 0-4; m is 0 or 1. Each of R_{10} and R_{11} is independently selected from hydrogen and C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-(C_1-C_8 alkyl). Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7. R_6 and R_7 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, (CO)-C_1-C_8 alkyl, aryl, heteroaryl, C_3-C_{10} cycloalkyl, or C_3-C_{10} (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R_6 and R_7 together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl. In formula (I), any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl, phenoxy, C_3-C_5 heteroaryl, or C_3-C_5 heteroaryloxy; or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Preferred embodiments of Formula (I) have a structure wherein: (a) R_1 is hydrogen, methyl, methoxy, fluoro, chloro, or bromo; (b) R_2 is hydrogen; (c) R_3, R_4, and R_5 independently are hydrogen, fluoro, chloro, bromo, iodo, methyl, methoxy, or nitro; (d) R_{10} and R_{11} independently are hydrogen or methyl; (e) Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7; R_6 and R_7 independently are hydrogen, C_{1-4} alkyl, heteroaryl, or C_{3-5} cycloalkyl optionally containing one or two heteroatoms selected from O, S, or NH; or R_6 and R_7 together with the nitrogen to which they are attached complete a 5-6 member cyclic ring optionally containing 1 or 2 additional heteroatoms selected from O, NH or N-alkyl; and wherein any of the foregoing alkyl or aryl groups can be unsubstituted or substituted by halo, hydroxy, methoxy, ethoxy, or heteroaryloxy

(such as the synthetic intermediate 2,3,4,5,6-pentafluorophenyl); (f) Z is $COOR_7$; (g) R_7 is H, pentafluorophenyl, or tetrazolyl; (h) R_3, R_4, and R_5 are independently H, fluoro, or chloro; (i) R_4 is fluoro; (j) two of R_3, R_4, and R_5 are fluoro; or (k) combinations of the above. In another preferred embodiment of Formula (I), R_1 is methyl, fluoro, chloro, or bromo.

Examples of preferred embodiments include methods comprising a MEK inhibitor selected from Formula (I) Compound Table below.

FORMULA (I) COMPOUND TABLE
(page 1 of 10)

[4-Chloro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine

[4-nitro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine

4-Fluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid

4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-2-methyl-phenylamino)-benzoic acid

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid

5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid

2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid

2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 2 of 10)

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide

N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide

3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 3 of 10)

4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide

N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 4 of 10)

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)-benzamide

5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 5 of 10)

5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide

5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide

(3-Hydroxy-pyrrolidin-1-yl)-[5-nitro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanone

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl-phenylamino)- benzamide

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl-phenylamino)- benzamide

N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide

5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 6 of 10)

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide

N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 7 of 10)

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(2 or 3-hydroxy-pyrrolidin-1-yl)-methanone

5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl)-methanone

N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 8 of 10)

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 9 of 10)

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 10 of 10)

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol

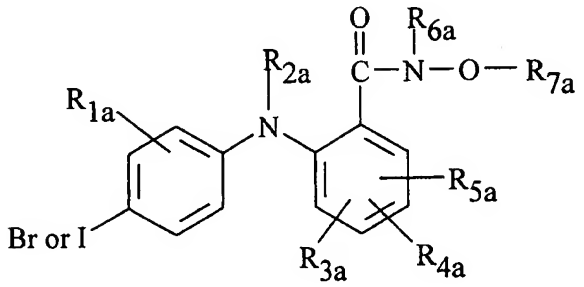
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol

[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

In another preferred embodiment, the MEK inhibitor is a compound of Formula II



II

In Formula (II), R_{1a} is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN. R_{2a} is hydrogen. Each of R_{3a}, R_{4a}, and R_{5a} is independently selected from hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, and (O or NH)$_m$-$(CH_2)_n$-R_{9a}. R_{9a} is hydrogen, hydroxy, CO_2H or $NR_{10a}R_{11a}$; n is 0-4; and m is 0 or 1. Each of R_{10a} and R_{11a} is independently hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-(C_1-C_8 alkyl). R_{6a} is hydrogen, C_1-C_8 alkyl, (CO)-(C_1-C_8 alkyl), aryl, aralkyl, or C_3-C_{10} cycloalkyl. R_{7a} is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{10} (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a}). In Formula (II), any of the alkyl, alkenyl, aryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl, phenoxy, C_3-C_5 heteroaryl, or C_3-C_5 heteroaryloxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or $NR_{10a}R_{11a}$. The invention also encompasses pharmaceutically acceptable salts, esters, amides or prodrugs of each of the disclosed compounds.

Preferred embodiments of Formula (II) are those structures wherein:

(a) R_{1a} is H, methyl, fluoro, or chloro; (b) R_{2a} is H; R_{3a}, R_{4a}, and R_{5a} are each H, Cl, nitro, or F; (c) R_{6a} is H; (d) R_{7a} is methyl, ethyl, 2-propenyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopropylmethyl, or cyclopropylethyl; (e) the 4' position is I, rather than Br; (f) R_{4a} is F at the 4 position, para to the CO-N-R_{6a}-OR_{7a} group and meta to the bridging nitrogen; (f) R_{3a} or R_{5a} is F; (g) at least one of R_{3a}, R_{4a}, and R_{5a} is F; (h) R_{1a} is methyl or chloro; or (i) a combination of the above.

In a more preferred embodiment the MEK inhibitor is a compound selected from Formula (II) Compound Table below.

FORMULA (II) COMPOUND TABLE
(page 1 of 7)

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 2 of 7)

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide

5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyloxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 3 of 7)

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide

5-Bromo-3-4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-ynyloxy)-benzamide

5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide

4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide

5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 4 of 7)

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-prop-2-ynyloxy)-benzamide
3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-2-ynyloxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 5 of 7)

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide

3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methyl-benzamide

2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 6 of 7)

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide

N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 7 of 7)

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide
N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide
2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide
2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide
2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide
2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide.

In the most preferred embodiment of this invention, a compound selected from the following is administered to a patient (ie, a mammal) in an amount that is effective to prevent or treat transplant rejection:

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD184352); 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD170611); 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD171984); 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD177168); 2-(2-Methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-5-bromobenzamide (PD 180841); 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 184161); 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD184386); 2-(2-Chloro-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluorobenzamide (PD 185625); 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD 185848); 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluorobenzamide (PD 188563); 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-

3,4,5-trifluorobenzamide (PD 198306); and 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide (PD 203311); and the benzoic acid derivatives thereof. For example, the benzoic acid derivative of PD 198306 is 2-(2-Methyl-4-iodophenylamino)-3,4,5-trifluorobenzoic acid.

Additional preferred compounds include 2-(2-chloro-4-iodophenylamino)-5-chloro-N-cyclopropylmethoxy -3,4-difluorobenzamide (PD 297189), 2-(4-iodophenylamino)-N-cyclopropylmethoxy-5-chloro-3,4-difluorobenzamide (PD 297190), 2-(4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296771), 2-(2-chloro-4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296770), 5-chloro-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid (PD 296767); and 5-chloro-N-cyclopropylmethoxy -3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide (PD 298127).

Another preferred method according to this invention comprises administering to a mammal that has undergone a transplant, or is about to undergo a transplant, the immunosuppressive agent which is 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide.

Still another preferred method according to this invention employs the compound which is 2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide.

The invention further provides methods of synthesis and synthetic intermediates.

Other features and advantages of the invention are apparent from the detailed description, examples, and claims set forth.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the dose response ability of 2-(2-chloro-4-iodophenylamino)-N-cycloproplymethoxy-3,4-difluorobenzamide (PD 184352) to inhibit the cellular production of interleukin-2 (IL-2) in human peripheral blood mononuclear cells stimulated with concanavalin A (Con A).

Figure 2 shows the dose response ability of PD 184352 to inhibit the cellular production of IL-2 in human peripheral blood mononuclear cells stimulated with anti-CD3 plus anti-CD28.

Figure 3 shows the dose response ability of PD 184352 to inhibit cellular production of interferon-δ (IFN-δ) in cells stimulated with Con A.

Figure 4 shows the ability of PD 184352 to suppress the human mixed lymphocyte reaction (MLR) as measured by the uptake of tritiated thymidine (3H-TDR).

Figure 5 shows the dose response ability of PD 184352 to inhibit Con A induced T-cell proliferation.

Figure 6 shows the dose response ability of PD 184352 to inhibit T-cell proliferation induced by phytohemagglutinin (PHA).

Figure 7 shows the lack of toxicity of PD 184352 in cells.

Figure 8 shows the inhibitory activity of several MEK inhibitors against MLR, IFN-gamma, and IL-2, and the ability of the compounds to inhibit PHA and Con A-induced proliferation with little or no toxicity (MTT). The compounds tested were PD 184352;

2-(2-methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD 171984);

2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 177168);

2-(2-chloro-4-iodophenylamino)-N-cycloproplymethoxy-3,4-difluoro-5-bromobenzamide (PD 184161); and

2-(2-chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD 184386).

Figure 9 shows the relative IL-2 suppressive activity of several phenyl amine compounds compared to rolipram and to dexamethasone (Dex).

Figure 10 shows the comparative activity of several phenyl amines, rolipram, and dexamethasone to suppress production of IFN-δ.

Figure 11 shows the human MLR suppressive activity of several phenyl amine MEK inhibitors compared to dexamethasone.

Figure 12 shows the ability of several phenyl amine MEK inhibitors to suppress human T-cell proliferation, compared to dexamethasone.

Figure 13 shows the percent cell death caused by several phenyl amine MEK inhibitors in the human MTT test.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a method for the prophylaxis of rejection of transplants in mammals, as well as control and maintenance of grafts. The invention is practiced by administering to a mammal that has undergone a transplant, or to a patient who is scheduled to undergo a transplant, an effective immunosuppressive amount of a selective MEK inhibitor to prevent or control the rejection of the transplanted organ, limb, cell(s), or tissue. For example, the method is practiced by administering a phenyl amine MEK inhibitor that is described in WO 98/37881. These are selective MEK inhibitors, namely they inhibit MEK 1 and MEK 2 without substantial inhibition of other enzymes. The method is ideally suited to prevent and control of rejection of kidney, liver, lung, and limb transplants.

The mammals to be treated according to this invention are patients who have undergone a transplant of an organ, a tissue, a limb, or cells, or who are about to undergo such transplant. Those skilled in the medical art are readily able to identify individual patients who are in need of an immunosuppressive agent in order to prevent or control the rejection of a foreign organ, limb, cell, or tissue.

The compounds of the present invention are MEK inhibitors. A MEK inhibitor is a compound that shows MEK inhibition when tested in the assays titled "Enzyme Assays" in United States Patent Number 5,525,625, column 6, beginning at line 35. The complete disclosure of United States Patent Number 5,525,625 is hereby incorporated by reference. An example of a MEK inhibitor is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran. Specifically, a compound is a MEK inhibitor if a compound shows activity in the assay titled "Cascade Assay for Inhibitors of the MAP Kinase Pathway," column 6, line 36 to column 7, line 4 of the United States Patent Number 5,525,625 and/or shows activity in the assay titled "In Vitro MEK Assay" at column 7, lines 4 to 27 of the above-referenced patent.

A. Terms

Some of the terms used herein are defined below in combination with their usage throughout this disclosure.

As used herein, the term "aryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from five to twelve carbon atoms. Examples of typical aryl groups include phenyl, naphthyl, and fluorenyl. The aryl may be substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Typical substituted aryl groups include 3-fluorophenyl, 3,5-dimethoxyphenyl, 4-nitronaphthyl, 2-methyl-4-chloro-7-aminofluorenyl, and the like.

The term "aryloxy" means an aryl group bonded through an oxygen atom, for example phenoxy, 3-bromophenoxy, naphthyloxy, and 4-methyl-1-fluorenyloxy.

"Heteroaryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from four to eleven carbon atoms and one, two, or three heteroatoms selected from O, S, or N. Examples include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, xanthenyl, pyronyl, indolyl, pyrimidyl, naphthyridyl, pyridyl, benzinnidazolyl, and triazinyl. The heteroaryl groups can be unsubstituted or substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Examples of substituted heteroaryl groups include chloropyranyl, methylthienyl, fluoropyridyl, amino-1,4-benzisoxazinyl, nitroisoquinolinyl, and hydroxyindolyl.

The heteroaryl groups can be bonded through oxygen to make heteroaryloxy groups, for example thienyloxy, isothiazolyloxy, benzofuranyloxy, pyridyloxy, and 4-methylisoquinolinyloxy.

The term "alkyl" means straight and branched chain aliphatic groups. Typical alkyl groups include methyl, ethyl, isopropyl, tert.-butyl, 2,3-dimethylhexyl, and 1,1-dimethylpentyl. The alkyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, as those terms are defined

herein. Typical substituted alkyl groups include chloromethyl, 3-hydroxypropyl, 2-dimethylaminobutyl, and 2-(hydroxymethylamino)ethyl. Examples of aryl and aryloxy substituted alkyl groups include phenylmethyl, 2-phenylethyl, 3-chlorophenylmethyl, 1,1-dimethyl-3-(2-nitrophenoxy)butyl, and 3,4,5-trifluoronaphthylmethyl. Examples of alkyl groups substituted by a heteroaryl or heteroaryloxy group include thienylmethyl, 2-furylethyl, 6-furyloxyoctyl, 4-methylquinolyloxymethyl, and 6-isothiazolylhexyl. Cycloalkyl substituted alkyl groups include cyclopropylmethyl, 2-cyclohexyethyl, piperidyl-2-methyl, 2-(piperidin-1-yl)-ethyl, 3-(morpholin-4-yl)propyl.

"Alkenyl" means a straight or branched carbon chain having one or more double bonds. Examples include but-2-enyl, 2-methyl-prop-2-enyl, 1,1-dimethyl-hex-4-enyl, 3-ethyl-4-methyl-pent-2-enyl, and 3-isopropyl-pent-4-enyl. The alkenyl groups can be substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, aryl, aryloxy, heteroaryl, or heteroyloxy, for example 2-bromoethenyl, 3-hydroxy-2-butenyl, 1-aminoethenyl, 3-phenylprop-2-enyl, 6-thienyl-hex-2-enyl, 2-furyloxy-but-2-enyl, and 4-naphthyloxy-hex-2-enyl.

"Alkynyl" means a straight or branched carbon chain having at least one triple bond. Typical alkynyl groups include prop-2-ynyl, 2-methyl-hex-5-ynyl, 3,4-dimethyl-hex-5-ynyl, and 2-ethyl-but-3-ynyl. The alkynyl groups can be substituted as the alkyl and alkenyl groups, for example, by aryl, aryloxy, heteroaryl, or heteroaryloxy, for example 4-(2-fluorophenyl)-but-3-ynyl, 3-methyl-5-thienylpent-4-ynyl, 3-phenoxy-hex-4-ynyl, and 2-furyloxy-3-methyl-hex-4-ynyl.

The alkenyl and alkynyl groups can have one or more double bonds or triple bonds, respectively, or a combination of double and triple bonds. For example, typical groups having both double and triple bonds include hex-2-en-4-ynyl, 3-methyl-5-phenylpent-2-en-4-ynyl, and 3-thienyloxy-hex-3-en-5-ynyl.

The term "cycloalkyl" means a nonaromatic ring or fused rings. Examples include cyclopropyl, cyclobutyl, cyclopenyl, cyclooctyl, bicycloheptyl, adamantyl, and cyclohexyl. The ring can optionally contain one, two, or three heteroatoms selected from O, S, or N. Such groups include tetrahydrofuryl, tetrahydropyrrolyl, octahydrobenzofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, octahydroindolyl, and octahydrobenzothiofuranyl. The cycloalkyl groups can be

substituted with the same substituents as an alkyl and alkenyl groups, for example, halo, hydroxy, aryl, and heteroaryloxy. Examples include 3-hydroxycyclohexyl, 2-aminocyclopropyl, 2-phenylpyrrolidinyl, and 3-thienylmorpholin-1-yl.

The term "maintenance" means controlling the tendency of a mammal to reject a cell, organ, limb, or tissue that has been transplanted into or onto the mammals body. The method is practiced by administering an amount of a selective MEK inhibitor that is effective to prevent or control the rejection.

The term "patient" means all animals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, horses, and pigs.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC_{50} for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC_{50} for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC_{50} that is at least 1/100, more preferably 1/500, and even more preferably 1/1000, 1/5000, or less than that of its IC_{50} or one or more of the above-named enzymes.

B. Administration and Formulation

The MEK inhibitors of the present method can be administered to a patient as part of a pharmaceutically acceptable composition. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as

ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part

of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalamic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present method can be administered to a patient at dosage levels in the range of about 0.1 to about 1000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kg of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

The compounds of the present method can be administered as pharmaceutically acceptable salts, esters, amides, or prodrugs. The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19 which is

incorporated herein by reference.)

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5 or 6 membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present method can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

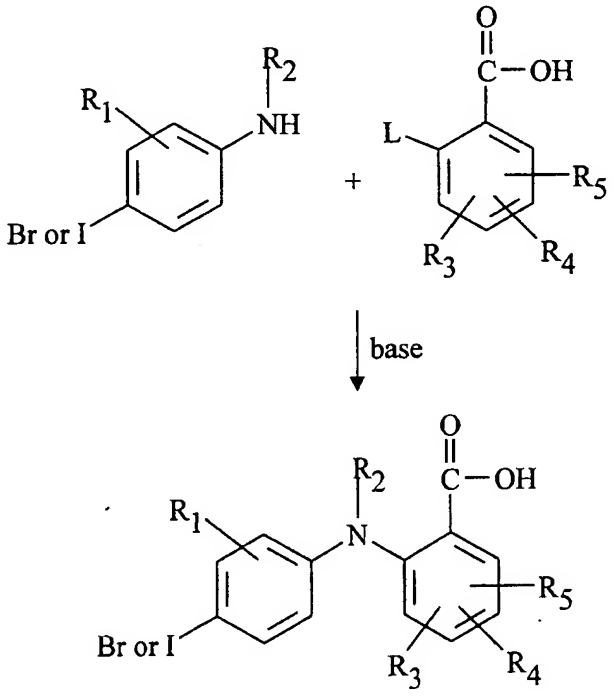
Some of the compounds of the present method can exist in different stereoisometric forms by virtue of the presence of chiral centers. It is contemplated that all stereoisometric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of this invention.

C. Synthesis

The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the specification, including the claims, in any way. After the priority date of the present disclosure, related syntheses and MEK inhibition data were also published in WO 99/01421 and WO 99/01426, hereby incorporated by reference.

The 2-(4-bromo and 4-iodo phenylamino)-benzoic acid derivatives of Formula (I) can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a benzoic acid having a leaving group at the 2-position to give a 2-(phenylamino)-benzoic acid. This process is depicted in Scheme 1.

Scheme 1



where L is a leaving group, for example halo such as fluoro.

The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of

the aniline in an unreactive organic solvent such as tetrahydrofuran or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium hydride, triethylamine, and Hunig's base. The reaction generally is carried out at a temperature of about -78°C to about 100°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

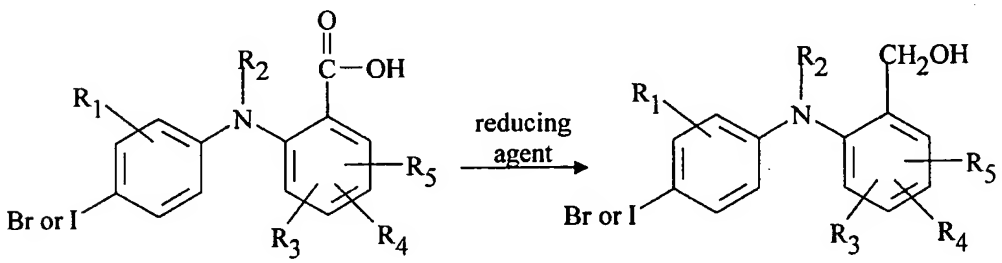
The 2-(phenylamino)-benzoic acid (e.g., Formula I, where R_7 is hydrogen) can be reacted with an organic or inorganic base such as pyridine, triethylamine, calcium carbonate, or sodium hydroxide to produce a pharmaceutically acceptable salt. The free acids can also be reacted with an alcohol of the formula HOR_7 (where R_7 is other than hydrogen, for example methyl) to produce the corresponding ester. Reaction of the benzoic acid with an alcohol can be carried out in the presence of a coupling agent. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)- phosphonium hexafluorophosphate (PyBrOP), and (benzotriazolyloxy) tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and alcohol derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

The benzamides of the invention, Formula (I)where Z is $CONR_6R_7$, are readily prepared by reacting the foregoing benzoic acids with an amine of the formula HNR_6R_7. The reaction is carried out by reacting approximately equimolar quantities of the benzoic acid and amine in an unreactive organic

solvent in the presence of a coupling reagent. Typical solvents are chloroform, dichloromethane, tetrahydrofuran, benzene, toluene, and xylene. Typical coupling reagents include DCC, EEDQ, PyBrOP, and PyBOP. The reaction is generally complete after about 10 minutes to about 2 hours when carried out at a temperature of about 0°C to about 60°C. The product amide is readily isolated by removing the reaction solvent, for instance by evaporation, and further purification can be accomplished by normal methods such as chromatography, crystallization, or distillation. The hydrazides (z = $CONHNR_{10}R_{11}$) are similarly prepared by coupling a benzoic acid with a hydrazine of the formula $H_2HNR_{10}R_{11}$.

The benzyl alcohols of the invention, compounds of Formula (I) where Z is CH_2OR_6 and R_6 is hydrogen, are readily prepared by reduction of the corresponding benzoic acid according to the following Scheme 2.

Scheme 2



Typical reducing agents commonly employed include borane in tetrahydrofuran. The reduction normally is carried out in an unreactive organic solvent such as tetrahydrofuran, and generally is complete within about 2 hours to about 24 hours when conducted at a temperature of about 0°C to about 40°C.

The following detailed examples illustrate specific compounds provided by this invention.

EXAMPLE 1

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid

To a stirring solution comprised of 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethenylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which temperature it was stirred for 2 days. The reaction mixture was concentrated. Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and then boiled over a steambath to low volume and cooled to room temperature. The off-white fibers were collected by vacuum filtration, rinsed with hexanes, and vacuum-oven dried. (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

^1H NMR (400 MHz; DMSO): δ 9.72 (s, 1H), 7.97 (dd, 1H, J = 7.0, 8.7 Hz), 7.70 (d, 1H, J = 1.5 Hz), 7.57 (dd, 1H, J = 8.4, 1.9 Hz), 7.17 (d, 1H, J = 8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

^{13}C NMR (100 MHz; DMSO): δ 169.87, 167.60, 165.12, 150.17, 150.05, 139.83, 138.49, 136.07, 135.31, 135.20, 135.07, 125.60, 109.32, 105.09, 104.87, 99.72, 99.46, 89.43, 17.52;

^{19}F NMR (376 MHz; DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C = O stretch) cm^{-1};

MS (CI) M+1 = 372.

Analysis calculated for $C_{14}H_{11}FINO_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

EXAMPLES 2-30

By following the general procedure of Example 1, the following benzoic acids and salts of Formula (I) were prepared.

Example No.	Compound	MP °C
2	3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	206-210
3	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	240.5-244.5
4	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	259.5-262
5	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	255-260
6	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	234-238
7	Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate	310-320 DEC
8	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	239.5-240
9	2-(2-Chloro-4-iodo-phenylamino)-5-nitro-benzoic acid	289-293
10	4-Fluoro-2-(3-fluoro-4-iodo-2-methyl-phenylamino)-benzoic acid	233-235
11	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid	264-267
12	2-(2-Fluoro-4-iodo-phenylamino)-5-nitro-benzoic acid	256-258
13	2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid	218.5-220
14	2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid	285-288 DEC
15	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid	230-234
16	3-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-221
17	3,4-Difluoro-2-(4-iodo-2-methoxy-phenylamino)-benzoic acid	230-233
18	4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	245-255 DEC

Example No.	Compound	MP °C
19	2-(4-Iodo-2-methyl-phenylamino)-benzoic acid	218-223
20	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	243-46
21	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	241-245
22	2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-222
23	4-Fluoro-2-(3-chloro-4-iodo-2-methyl-phenylamino)-benzoic acid	248-252.5
24	2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid	208-211
25	3-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	232-233
26	2-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	179-182
27	4-Fluoro2-(2,3-dimethyl-4-iodo-2-methyl-phenylamino)benzoic acid	258-261
28	5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	209.5-211
29	2-Chloro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	171-175
30	2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid	251-263

EXAMPLE 31

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirring solution comprised of 0.1020 g (0.2632 mmol) of 5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid, 0.1 mL (1.7 mmol) of ethanolamine, and 0.05 mL (0.29 mmol) of diisopropylethylamine in 5 mL of a 1:1 (v/v) tetrahydrofuran-dichloromethane solution was added 0.15 g (0.29 mmol) of solid PyBOP powder directly. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The crude residue was partitioned between ether (50 mL) and 10% aqueous hydrochloric acid (50 mL). The organic phase was washed with 10% aqueous sodium hydroxide (50 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a yellow-brown oil which was crystallized from hexanes-ether to afford 0.0831 g (73%) of a green-yellow powder; mp 120-121°C;

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.11 (s, 1H), 7.56 (d, 1H, J = 1.4 Hz), 7.46-7.41 (m, 2H), 7.20 (dd, 1H, J = 8.9, 2.4 Hz), 7.00 (t, 2H, J = 9.6 Hz), 6.55 (broad t, 1H), 3.86 (t, 2H, J = 5.0 Hz), 3.61 (dd, 2H, J = 10.1, 5.5 Hz), 2.23 (s, 3H), 1.56 (broad s, 1H);

IR (KBr) 3297 (O-H stretch), 1627 (C = O stretch) cm^{-1};

MS (CI) M+1 = 431.

Analysis calculated for $C_{16}H_{16}ClIN_2O_2$:

C, 44.62; H, 3.74; N, 6.50.

Found: 44.63; H, 3.67; N, 6.30.

EXAMPLES 32-48

By following the general procedure of Example 31, the following benzamides were prepared by reacting the corresponding benzoic acid with the corresponding amine.

Example No.	Compound	MP °C
32	4-Methoxy-N-(4-methoxy-phenyl)-3-nitro-benzamide	153.5-156
33	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	158
34	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide	102.5-104.5
35	N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	90-91
36	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	oil
37	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide	285-288 DEC
38	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	180-182
39	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	137-138

Example No.	Compound	MP °C
40	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	170-173
41	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide	69-71
42	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	132-133.4
43	N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	oil
44	4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide	122-124
45	N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	91-93
46	N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	97-99
47	5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	118-120
48	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	142.5-144

EXAMPLE 49

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.50 g, 1.35 mmol) was dissolved in 6 mL (6 mmol) of cold 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran solution. The reaction mixture was stirred under nitrogen atmosphere at room temperature overnight. The reaction was quenched with 80 mL of methanol. Concentration in vacuo produced a clear tan oil which was purified by MPLC. Elution with dichloromethane afforded 0.4285 g (89%) of a white solid; mp 99-100.5°C;

^{1}H NMR (400 MHz; DMSO): δ 7.57 (d, 1H, J=1.7 Hz), 7.45 (dd, 1H, J=8.4, 1.9 Hz), 7.39 (s, 1H), 7.29 (t, 1H, J=7.5 Hz), 6.89 (d, 1H, J=8.4 Hz), 6.67-6.60 (m, 1H), 5.47 (t, 1H, J=5.5 Hz), 4.49 (d, 2H, 5.1 Hz), 2.14 (s, 3H);

IR (KBr) 3372 (O-H stretch) cm^{-1};

MS (CI) M+1 = 358.

Analysis calculated for $C_{14}H_{13}FINO$:

C, 47.08; H, 3.67; N, 3.92.

Found: C, 47.17; H, 3.75; N, 3.72.

EXAMPLE 50-52

The following benzyl alcohols were prepared by the general procedure of Example 49.

Example No.	Compound	MP °C
50	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	82-85
51	[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol	126.5-128.5
52	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	60.5-63.5

Several invention compounds of Formula (I) were prepared utilizing combinatorial synthetic techniques. The general procedure is as follows:

To a 0.8-mL autosampler vial in a metal block was added 40 μL of a 0.5 M solution of the acid in DMF and 40 μL of the reagent amine (2 M solution in Hunig's base and 1 M in amine in DMF). A 0.5 M solution of PyBrop was freshly prepared and 50 μL were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm × 25 cm, 5 μM spherical silica, pore size 115 A derivatized with C-18, the sample was eluted at 4.7 mL/min with

a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes). Fractions were collected by monitoring at 214 nM. The residue was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield.

EXAMPLES 53-206

The following compounds of Formula I were prepared by combinatorial methodology:

Example No.	Compound	MS M-H
53	5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	510
54	N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	462
55	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	577
56	3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	432
57	N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	444
58	3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	446
59	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	564
60	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	571
61	4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	414
62	5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	551

Example No.	Compound	MS M-H
63	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	580
64	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	501
65	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	485
66	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	493
67	N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
68	N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	460
69	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide	384
70	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	483
71	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	495
72	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	513
73	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide	480
74	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	467
75	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide	453
76	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	557
77	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	479
78	2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide	425

Example No.	Compound	MS M-H
79	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	461
80	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	475
81	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide	445
82	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide	400
83	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	437
84	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide	474
85	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide	450
86	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide	431
87	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide	444
88	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide	451
89	5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	557*
90	5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	541*
91	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide	487
92	5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	601*
93	5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	486*

Example No.	Compound	MS M-H
94	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	497*
95	(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanone	466
96	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	484*
97	5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	530*
98	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide	518*
99	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide	562*
100	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone	499
101	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid phenethyl ester	501
102	N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide	568*
103	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone	455
104	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	460
105	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	528*
106	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	542*
107	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	468*
108	5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	472*
109	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide	502*

Example No.	Compound	MS M-H
110	5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	445*
111	5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	516*
112	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	482*
113	5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	489*
114	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	556*
115	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide	529*
116	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	500*
117	5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	500*
118	5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	514*
119	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	512*
120	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide	509*
121	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide	544*
122	N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	470*
123	5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	516*
124	N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	456*
125	5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429*

Example No.	Compound	MS M-H
126	N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	484*
127	N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	511*
128	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	544*
129	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide	523*
130	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone	439
131	5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	558*
132	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	484*
133	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	496*
134	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-	482
135	N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide	500*
136	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	443
137	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	495*
138	N-(3-Dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	483*
139	N-(2-Diisopropylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide	498*
140	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	490
141	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	506

Example No.	Compound	MS M-H
142	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	536
143	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-thiobenzoic acid S-benzyl ester	503
144	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	476
145	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	492
146	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409
147	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429
148	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	413
149	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	475
150	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	593*
151	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	567
152	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
153	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	521

Example No.	Compound	MS M-H
154	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	440
155	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	486
156	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
157	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	459
158	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409
159	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	583
160	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	538
161	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
162	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436
163	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	469
164	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	475
165	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	646
166	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	598
167	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436

Example No.	Compound	MS M-H
168	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	565
169	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	469
170	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	473
171	N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
172	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	519
173	N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	502
174	N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	559
175	N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
176	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	581
177	2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide	500
178	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	567
179	N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	451
180	5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	467
181	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	533
182	5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	511
183	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	489
184	N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	478

Example No.	Compound	MS M-H
185	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	538
186	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	477
187	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	431
188	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	475
189	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	488
190	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	477
191	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	523
192	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
193	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	427
194	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	461
195	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	442
196	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	415
197	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
198	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411
199	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	540
200	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438
201	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411

Example No.	Compound	MS M-H
202	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	585
203	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
204	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	601
205	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	522
206	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438

* M+H

EXAMPLE 207

Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

Step a: Preparation of 5-chloro-2-fluoro-benzaldehyde

To a solution of 1-chloro-4-fluorobenzne (13.06 g, 0.1 mol) in THF (180 mL), at -78°C, LDA (2M solution in THF, 50 mL, 0.1 mol) was added drop wise. After stirring at -78°C for 1.5 hours, DMF (8 mL) was added to the reaction mixture and allowed to warm up to room temperature overnight. The reaction mixture was partitioned between water and Et_2O. The Et_2O layer was dried ($MgSO_4$) and the solvent removed in vacuum to give 14.95 g (94%) yield of crude aldehyde: ^1H NMR ($CDCl_3$): δ, 10.3 (s, -C(=O)H).

Step b: Preparation of 5-chloro-2-fluoro-benzaldehyde oxime

A solution of 5-chloro-2-fluoro-benzaldehyde (10 g, 0.0631 mol), hydroxylamine hydrochloride (6.57 g, 0.0946 mol) and pyridine (8.3 mL, 0.1010 mol) in EtOH (100 mL) was heated at 75°C (oil bath temperature) for 1 hour and the solvent removed under vacuum to give an oil. The oil was partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and the solvent removed under vacuum to give crude aldoxime as a solid. The

solid was purified by medium pressure liquid chromatography on silica. Elution with CH_2Cl_2 gave 4.87 g (28%) of the aldoxime as white solid: mp 95-97°C;

Analysis calculated for C_7H_5NOFCl:

C, 48.44; H, 2.90; N, 8.07.

Found: C, 48.55; H, 2.69, N, 7.90.

Step c: Preparation of 5-chloro-2-fluoro-benzonirile

A solution of the 5-chloro-2-fluoro-benzaldehyde oxime (3.15 g, 0.0182 mol) in acetic anhydride (150 mL) was refluxed for 16 hours. The reaction mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (200 mL) solution. The mixture was extracted with Et_2O. The Et_2O layer was dried (K_2CO_3) and the solvent removed to give the product as an oily solid. The product was used without further purification in the next step.

Step d: Preparation of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole

A mixture of 5-chloro-2-fluoro-benzonitrile (2.84 g, 0.01823 mol), butanol (15 mL), sodium azide (1.543 g, 0.0237 mol), acetic acid (1.36 mL, 0.0237 mol) was refluxed for 24 hours. The reaction mixture was cooled to room temperature, additional 1.543 g sodium azide added, and the reaction mixture refluxed for additional 24 hours. After cooling to room temperature, Et_2O (100 mL) and 10% aqueous NaOH (200 mL) were added sequentially. The mixture was vigorously stirred. The aqueous layer was separated, cooled with ice-methanol bath (-15°C) and acidified to pH 1 with conc. HCl. A gray solid precipitated. The solid was dried in vacuum at 50°C to give 1.76 g (49%) of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole: mp partial melt at 110°C, complete melting at 124°C);

^1H (400 Mz, $CDCl_3$): δ 8.19-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.61-7.52 (m, 1H);

^{13}C (100 Mz, $CDCl_3$): δ 159.00, 156.49, 140.88, 133.02, 132.93, 130.73, 129.23, 129.21, 129.08, 126.05, 118.96, 118.73, 114.50;

MS (CI) M+1 = 199 (100), M = 198 (6).

Step e: Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

To a solution of 2-methyl-4-iodoaniline (3.52 g, 0.0151 mol) in THF (25 mL) at -78°C, LDA (2 molar solution in THF, 11.33 mL, 0.02267 mol) was added dropwise. After stirring for 0.5 hours, a solution of 1-(tetrazol-5-yl)-2-fluoro-5-chlorobenzene (1.5 g, 0.00756 mol) in THF (15 mL) was added dropwise. The reaction was stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous conc. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent removed giving a crude product as an oil. The oil with CH_2Cl_2->CH_2Cl_2:MeOH (9.7:0.3) gave 1.5 g (48%) of the desired product:

mp 205-208°C; ^1H (400 Mz, DMSO): δ 9.13 (s, 1H), 8.00-7.99 (s, 1H), 7.69 (s, 1H), 7.55-7.52 (m, 1H), 7.43-7.40 (m, 1H), 7.12-7.05 (m, 1H), 2.24 (s, 3H); ^{13}C (100 Mz, $CDCl_3$): δ 141.87, 139.28, 138.88, 135.47, 133.71, 131.65, 128.15, 123.69, 121.94, 116.68, 87.79, 17.22; MS (CI) M+2 = 413 (44), M+1 = 412 (85), M = 411 (100).

Analysis calculated for $C_{14}H_{11}N_5ClI \cdot 0.5H_2O$:

C, 39.97; H, 2.87; N, 16.65.

Found: C, 38.87, H, 2.77; N, 16.47.

The following tetrazole substituted phenylamines were prepared by following the general procedure of Example 207.

EXAMPLE 208

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine, mp 231°C (dec)

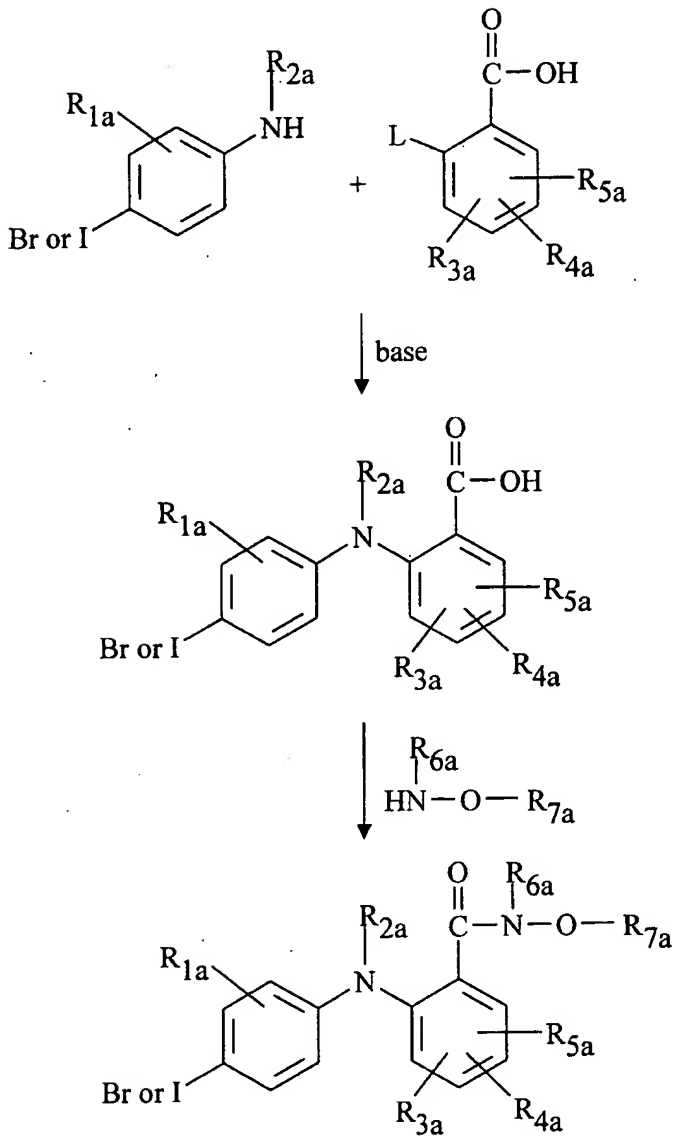
EXAMPLE 209

[4-nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine, mp 205-208°C.

The 4-bromo and 4-iodo phenylamino benzhydroxamic acid derivatives of Formula II can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic

chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a benzoic acid having a leaving group at the 2-position to give a phenylamino benzoic acid, and then reacting the benzoic acid phenylamino derivative with a hydroxylamine derivative (Scheme 3).

Scheme 3



where L is a leaving group, for example halo such as fluoro, chloro, bromo or iodo, or an activated hydroxy group such as a diethylphosphate, trimethylsilyloxy, p-nitrophenoxy, or phenylsulfonoxy.

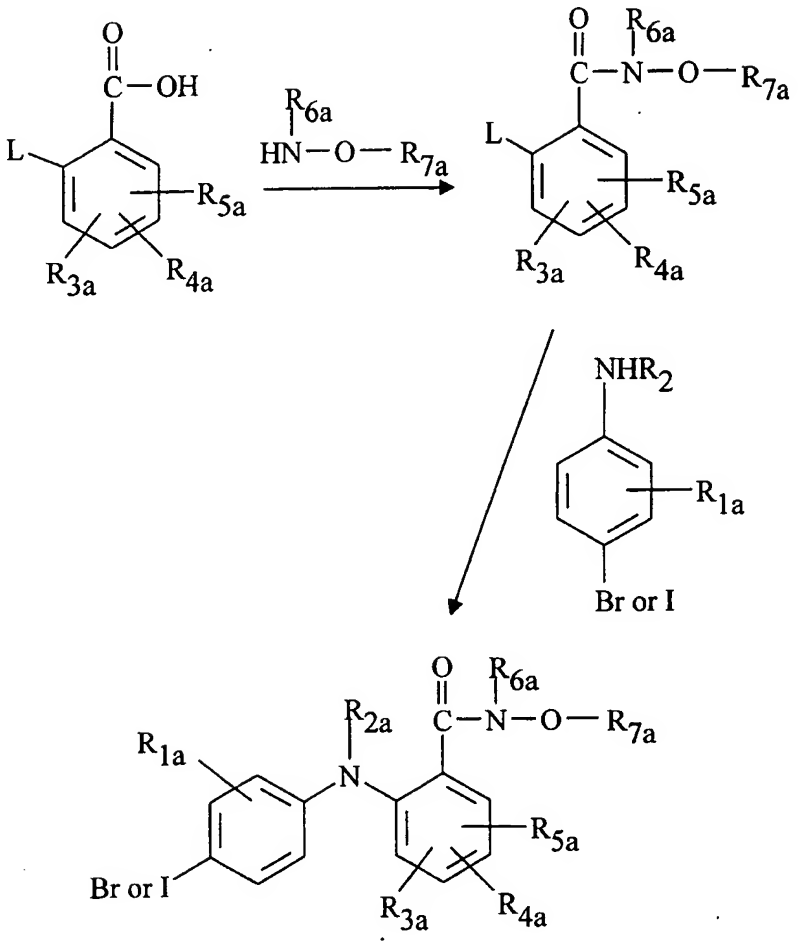
The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of the aniline in an unreactive organic solvent such as tetrahydrofuran, or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium hydride, and sodium amide. The reaction generally is carried out at a temperature of about -78°C to about 25°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

The phenylamino benzoic acid next is reacted with a hydroxylamine derivative $HNR_{6a}OR_{7a}$ in the presence of a peptide coupling reagent. Hydroxylamine derivatives that can be employed include methoxylamine, N-ethyl-isopropoxy amine, and tetrahydro-oxazine. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBrOP) and (benzotriazolyloxy)tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and hydroxylamino derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

An alternative method for making the invention compounds involves first converting a benzoic acid to a hydroxamic acid derivative, and then reacting the

hydroxamic acid derivative with an aniline. This synthetic sequence is depicted in Scheme 4.

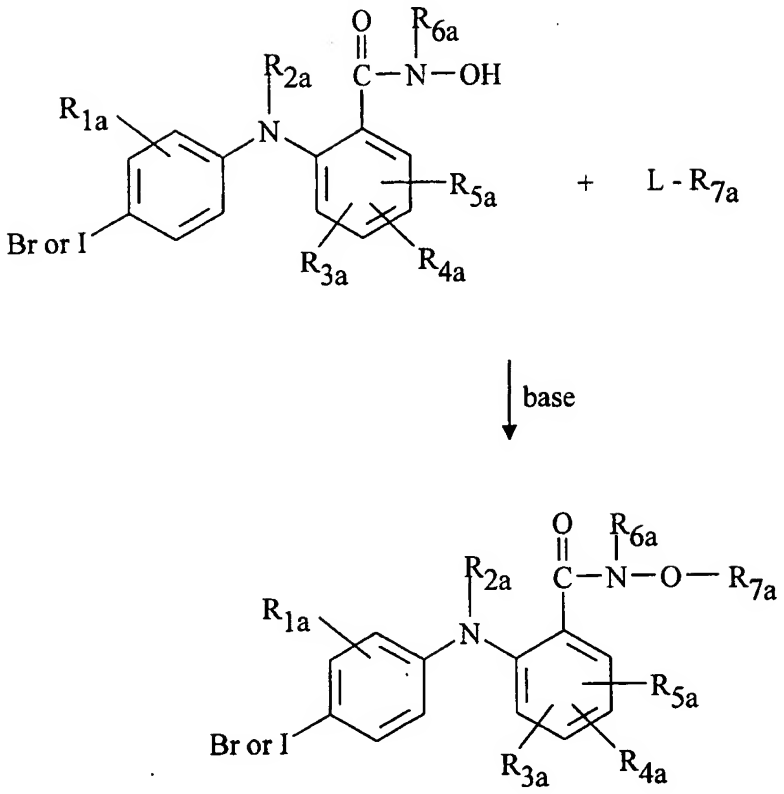
Scheme 4



where L is a leaving group. The general reaction conditions for both of the steps in Scheme 4 are the same as those described above for Scheme 3.

Yet another method for making invention compounds comprises reacting a phenylamino benzhydroxamic acid with an ester forming group as depicted in Scheme 5.

Scheme 5



where L is a leaving group such as halo, and a base is triethylamine or diisopropylamine.

The synthesis of compounds of Formula (II) is further illustrated by the following detailed examples.

EXAMPLE 1a

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

(a) Preparation of 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

To a stirred solution containing 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which

temperature the mixture was stirred for 2 days. The reaction mixture was concentrated by evaporation of the solvent under reduced pressure. Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and then concentrated over a steambath to low volume (10 mL) and cooled to room temperature. The off-white fibers which formed were collected by vacuum filtration, rinsed with hexane, and dried in a vacuum-oven (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

^1H NMR (400 MHz, DMSO): δ 9.72 (s, 1H), 7.97 (dd, 1H, J=7.0, 8.7 Hz), 7.70 (d, 1H, J=1.5 Hz), 7.57 (dd, 1H, J=8.4, 1.9 Hz), 7.17 (d, 1H, J=8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 169.87, 166.36 (d, J_{C-F}=249.4 Hz), 150.11 (d, J_{C-F}=11.4 Hz), 139.83, 138.49, 136.07, 135.26 (d, J_{C-F}=11.5 Hz), 135.07, 125.60, 109.32, 104.98 (d, J_{C-F}=21.1 Hz), 99.54 (d, J_{C-F}=26.0 Hz), 89.43, 17.52;

^{19}F NMR (376 MHz, DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C=O stretch)cm^{-1};

MS (CI) M+1 = 372.

Analysis calculated for $C_{14}H_{11}FINO_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

(b) Preparation of 4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirred solution of 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.6495 g, 0.001750 mol), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.2590 g, 0.002211 mol), and diisopropylethylamine (0.40 mL, 0.0023 mol) in 31 mL of an equivolume tetrahydrofuran-dichloromethane solution was added 1.18 g (0.00227 mol) of solid PyBOP ([benzotriazolyloxy]tripyrrolidino phosphonium hexafluorophosphate, Advanced ChemTech) directly. The reaction mixture was stirred for 30 minutes after which time it was concentrated in vacuo. The brown oil was treated with 10% aqueous hydrochloric acid. The suspension

was extracted with ether. The organic extraction was washed with 10% sodium hydroxide followed by another 10% hydrochloric acid wash, was dried ($MgSO_4$) and concentrated in vacuo to afford 1.0 g of a light-brown foam. This intermediate was dissolved in 25 mL of ethanolic hydrogen chloride, and the solution was allowed to stand at room temperature for 15 minutes. The reaction mixture was concentrated in vacuo to a brown oil that was purified by flash silica chromatography. Elution with a gradient (100 % dichloromethane to 0.6 % methanol in dichloromethane) afforded 0.2284 g of a light-brown viscous oil. Scratching with pentane-hexanes and drying under high vacuum afforded 0.1541 g (23%) of an off-white foam; mp 61-75°C;

^1H NMR (400 MHz, DMSO): δ 11.34 (s, 1H), 9.68 (s, 1H), 9.18 (s, 1H), 7.65 (d, 1H, J=1.5 Hz), 7.58 (dd, 1H, J=8.7, 6.8 Hz), 7.52 (dd, 1H, J=8.4, 1.9 Hz), 7.15 (d, 1H, J=8.4 Hz), 6.74 (dd, 1H, J=11.8, 2.4 Hz), 6.62 (ddd, 1H, J=8.4, 8.4, 2.7 Hz), 2.18 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 165.91, 164.36 (d, J_{C-F}=247.1 Hz), 146.78, 139.18, 138.77, 135.43, 132.64, 130.60 (d, J_{C-F}=11.5 Hz), 122.23, 112.52, 104.72 (d, J=22.1 Hz), 100.45 (d, J_{C-F}=25.2 Hz), 86.77, 17.03;

^{19}F NMR (376 MHz, DMSO): δ -107.20 to -107.27 (m);

IR (KBr) 3307 (broad, O-H stretch), 1636 (C=O stretch) cm^{-1};

MS (CI) M+1 = 387.

Analysis calculated for $C_{14}H_{12}FIN_2O_2$:

C, 43.54; H, 3.13; N, 7.25.

Found: C, 43.62; H, 3.24; N, 6.98.

EXAMPLE 2a

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

(a) Preparation of 5-Bromo-2,3,4-trifluorobenzoic acid

To a stirred solution comprised of 1-bromo-2,3,4-trifluorobenzene (Aldrich, 99%; 5.30 g, 0.0249 mol) in 95 mL of anhydrous tetrahydrofuran cooled to -78°C was slowly added 12.5 mL of 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene solution (Aldrich). The mixture was stirred

for 1 hour and transferred by canula into 700 mL of a stirred saturated ethereal carbon dioxide solution cooled to -78°C. The cold bath was removed, and the reaction mixture was stirred for 18 hours at ambient temperature. Dilute (10%) aqueous hydrochloric acid (ca. 500 mL) was poured into the reaction mixture, and the mixture was subsequently concentrated on a rotary evaporator to a crude solid. The solid product was partitioned between diethyl ether (150 mL) and aq. HCl (330 mL, pH 0). The aqueous phase was extracted with a second portion (100 mL) of diethyl ether, and the combined ethereal extracts were washed with 5% aqueous sodium hydroxide (200 mL) and water (100 mL, pH 12). These combined alkaline aqueous extractions were acidified to pH 0 with concentrated aqueous hydrochloric acid. The resulting suspension was extracted with ether (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and subjected to high vacuum until constant mass was achieved to afford 5.60 g (88% yield) of an off-white powder; mp 139-142.5°C;

^1H NMR (400 MHz, DMSO): δ 13.97 (broad s, 1H, 8.00-7.96 (m, 1H);

^{13}C NMR (100 MHz, DMSO): δ 162.96, 129.34, 118.47, 104.54 (d, J_{C-F}=22.9 Hz);

^{19}F NMR (376 MHz, DMSO): δ -120.20 to -120.31 (m), -131.75 to -131.86 (m), -154.95 to -155.07 (m);

IR (KBr) 1696 (C=O stretch)cm^{-1};

MS (CI) M+1 = 255.

Analysis calculated for $C_{74}H_{21}BrF_3O_2$:

C, 32.97; H, 0.79; N, 0.00; Br, 31.34; F, 22.35.

Found: C, 33.18; H, 0.64; N, 0.01; Br, 30.14; F, 22.75.

(b) <u>Preparation of 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid</u>

To a stirred solution comprised of 1.88 g (0.00791 mol) of 2-amino-5-iodotoluene in 10 mL of tetrahydrofuran at -78°C was added 6 mL (0.012 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for

10 minutes, after which time a solution of 1.00 g (0.00392 mol) of 5-bromo-2,3,4-trifluorobenzoic acid in 15 mL of tetrahydrofuran was added. The cold bath was subsequently removed, and the reaction mixture stirred for 18 hours. The mixture was concentrated, and the concentrate was treated with 100 mL of dilute (10%) aqueous hydrochloric acid. The resulting suspension was extracted with ether (2 × 150 mL), and the combined organic extractions were dried ($MgSO_4$) and concentrated in vacuo to give an orange solid. The solid was triturated with boiling dichloromethane, cooled to ambient temperature, and collected by filtration. The solid was rinsed with dichloromethane, and dried in the vacuum-oven (80°C) to afford 1.39 g (76%) of a yellow-green powder; mp 259.5-262°C;

^1H NMR (400 MHz, DMSO): δ 9.03 (s, 1H), 7.99 (dd, 1H, J=7.5, 1.9 Hz), 7.57 (dd, 1H, J=1.5 Hz), 7.42 (dd, 1H, J=8.4, 1.9 Hz), 6.70 (dd, 1H, J=8.4, 6.0 Hz), 2.24 (s, 3H);

^{19}F NMR (376 MHz, DMSO): δ -123.40 to -123.47 (m); -139.00 to -139.14 (m);

IR (KBr) 1667 (C=O stretch)cm^{-1};

MS (CI) M+1 = 469.

Analysis calculated for $C_{14}H_9BrF_2INO_2$:

C, 35.93; H, 1.94; N, 2.99; Br, 17.07; F, 8.12; I, 27.11.

Found: C, 36.15; H, 1.91; N, 2.70; Br, 16.40; F, 8.46; I, 26.05.

(c) Preparation of 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirred solution comprised of 5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.51 g, 0.0011 mol), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.15 g, 0.0013 mol), and diisopropylethylamine (0.25 mL, 0.0014 mol) in 20 mL of an equivolume tetrahydrofuran-dichloromethane solution was added 0.6794 g (0.001306 mol) of solid PyBOP (Advanced ChemTech) directly. The reaction mixture was stirred at 24°C for 10 minutes, and then was concentrated to dryness in vacuo. The concentrate was suspended in 100 mL of 10% aqueous hydrochloric acid. The suspension was extracted with 125 mL of diethyl ether. The ether layer was separated, washed with 75 mL of 10% aqueous sodium hydroxide, and then with 100 mL of dilute

acid. The ether solution was dried ($MgSO_4$) and concentrated in vacuo to afford 0.62 g (100%) of an off-white foam. The foam was dissolved in ca. 15 mL of methanolic hydrogen chloride. After 5 minutes, the solution was concentrated in vacuo to an oil, and the oil was purified by flash silica chromatography. Elution with dichloromethane: dichloromethane-methanol (99:1) afforded 0.2233 g (42%) of a yellow powder. The powder was dissolved in diethyl ether and washed with dilute hydrochloric acid. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 0.200 g of a foam. This product was triturated with pentane to afford 0.1525 g of a powder that was repurified by flash silica chromatography. Elution with dichloromethane afforded 0.0783 g (15%) of an analytically pure title compound, mp 80-90°C;

^1H NMR (400 MHz, DMSO): δ 11.53 (s, 1H), 9.38 (s, 1H), 8.82 (s, 1H), 7.70 (dd, 1H, J=7.0, 1.9 Hz), 7.53 (s, 1H), 7.37 (dd, 1H, J=8.4, 1.9 Hz), 6.55 (dd, 1H, J=8.2, 6.5 Hz), 2.22 (s, 3H);

^{19}F NMR (376 MHz, DMSO): δ -126.24 to -126.29 (m), -137.71 to -137.77 (m);

IR (KBr) 3346 (broad, O-H stretch), 1651 (C=O stretch)cm^{-1};

MS (CI) M+1 = 484.

Analysis calculated for $C_{14}H_{10}BrF_2IN_2O_2$:

C, 34.81; H, 2.09; N, 5.80.

Found: C, 34.53; H, 1.73; N, 5.52.

Examples 3a to 12a in the table below were prepared by the general procedure of Examples 1a and 2a.

EXAMPLES 13a-77a

Examples 13a to 77a were prepared utilizing combinatorial synthetic methodology by reacting appropriately substituted phenylamino benzoic acids

(e.g., as shown in Scheme 1) and hydroxylamines (e.g., (NHR_{6a})-O-R_{7a}). A general method is given below:

To a 0.8-mL autosampler vial in a metal block was added 40 μL of a 0.5 M solution of the acid in DMF and 40 μL of the hydroxylamine (2 M solution

in Hunig's base and 1 M in amine in DMF). A 0.5 M solution of PyBrOP was freshly prepared, and 50 μL were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm × 25 cm, 5 μM spherical silica, pore Size 115 A derivatized with C-18, the sample was eluted at 4.7 mL/min with a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes.) Fractions were collected by monitoring at 214 nM. The desired fractions were evaporated using a Zymark Turbovap. The product was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield. The structure was confirmed by mass spectroscopy.

EXAMPLES 3a-77a

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
3a	2-(4-bromo-2-methyl-phenylamino)-4-fluoro-N-hydroxy-benzamide	56-75 dec	523
4a	5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide	65 dec	
5a	5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide	62-67	
6a	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(terahydropyran-2-yloxy)benzamide	105-108	
7a	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxybenzamide	64-68	
8a	4-Fluoro-N-hydroxy-2-(4-fluoro-2-methyl-phenylamino)-benzamide	119-135	
9a	4-Fluoro-N-hydroxy-2-(2-methyl phenylamino)-benzamide	101-103	
10a	4-Fluoro-2-(4-fluor-2-methyl-phenylamino)-N-(terahydropyran-2-yloxy)benzamide	142-146	
11a	4-Fluoro-N-hydroxy-2-(4-cluoro-2-methyl-phenylamino)-benzamide	133.5-135	

Example No:	Compound	Melting Point (°C)	MS ($M-H^+$)
12a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide	107-109.5	
13a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide		399
14a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide		417
15a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-methoxy-benzamide		369
16a	2-(4-Bromo-2-methyl-phenylamino)-N-ethoxy-3,4-difluoro-benzamide		342* (M-EtO)
17a	5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		509
18a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		445
19a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-isopropoxy-benzamide		397
20a	4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		465

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
21a	3,4-Difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		483
22a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(furan-3-ylmethoxy)-benzamide		435
23a	5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		561
24a	5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		536
25a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		423
26a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		441
27a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide		455
28a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(1-methyl-prop-2-ynyloxy)-benzamide		407
29a	N-(But-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		455

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
30a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-3,4-difluoro-benzamide		407
31a	5-Bromo-N-(but-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		533
32a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenyl-prop-2-ynyloxy)-benzamide		517
33a	3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenyl-prop-2-ynyloxy)-benzamide		469
34a	3,4-Difluoro-N-[3-(3-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		535
35a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-[3-(3-fluoro-phenyl)-prop-2-ynyloxy]-benzamide		487
36a	3,4-Difluoro-N-[3-(2-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		535
37a	5-Bromo-3,4-difluoro-N-[3-(2-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		613

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
38a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenyl-pent-2-en-4-ynyloxy)-benzamide		557* *(M+H)
39a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-methyl-5-phenyl-pent-2-en-4-ynyloxy)-benzamide		510
40a	N-Ethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		431
41a	2-(4-Bromo-2-methyl-phenylamino)-N-ethoxy-3,4-difluoro-benzamide		383
42a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		427
43a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		445
44a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-propoxy-benzamide		397
45a	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		523
46a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		427

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
47a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		445
48a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-isopropoxy-benzamide		397
49a	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		523
50a	N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457
51a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclobutyloxy-3,4-difluoro-benzamide		409
52a	N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		453
53a	N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		471
54a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclopentyloxy-3,4-difluoro-benzamide		423
55a	N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		439
56a	N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
57a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide		409
58a	5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)		435
59a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxy-ethoxy)-benzamide		505
60a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxy-ethoxy)-benzamide		523
61a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-phenoxy-ethoxy)-benzamide		475
62a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiophen-2-ylmethoxy)-benzamide		481
63a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiophen-2-ylmethoxy)-benzamide		499
64a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)-benzamide		451
65a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-allyloxy)-benzamide		439

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
66a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-allyloxy)-benzamide		457
67a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-methyl-allyloxy)-benzamide		410
68a	N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		439
69a	N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457
70a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-3,4-difluoro-benzamide		410
71a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		441
72a	N-(But-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		455
73a	2-(4-Bromo-2-methyl-phenylamino)-N-(4,4-dimethyl-pent-2-ynyloxy)-3,4-difluoro-benzamide		449
74a	N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
75a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-3,4-difluoro-benzamide		410
76a	N-(3-tert-butyl-propyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		479
77a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide		577

PHYSICAL DATA FOR SELECTED COMPOUNDS

PD 0171984

mp 80-90 °C

PD 0184161

mp 174-175 °C

PD 0203311

mp 141-144 °C

PD 0297189

mp 167-169 °C

^{1}H-NMR (400 MHz; DMSO) δ 11.70 (s, 1H), 8.59 (s, 1H), 7.55 (s, 1H), 7.43 (d, 1H, J=6.5 Hz), 7.27 (d,1H, J=8.7 Hz), 6.46 (m, 1H), 3.42 (d, 2H, J=7.0 Hz), 0.84 (m, 1H), 0.27 (m, 2H), 0.00 (m, 2H)

PD 0297190

mp 125.5-133 °C

^{1}H-NMR (400 MHz; DMSO) δ 11.48 (s, 1H), 8.32 (s, 1H), 7.34 (d, 1H, J=7.5 Hz), 7.28 (d, 2H, J=8.2 Hz), 6.48 (d, 2H, J=7.7 Hz), 3.32 (d, 2H, J=6.8 Hz), 0.81 (m, 1H), 0.28 (m, 2H), 0.00 (m, 2H)

PD 0296771

mp 266.7-268.9 °C

^{1}H-NMR (400 MHz; DMSO) δ 13.85 (broad s, 1H), 8.99 (s, 1H), 7.87 (dd, 1H, J=7.9, 2.1 Hz), 7.55 (d,2H, J=8.6 Hz), 6.82 (dd, 2H, J=8.7, 2.8 Hz)

PD 0296770

mp 293.2-296.3 °C

^{1}H-NMR (400 MHz; DMSO) δ 14.05 (broad s, 1H), 9.21 (s, 1H), 7.93 (dd, 1H, J=7.8, 2.2 Hz), 7.82 (d,1H, J=1.9 Hz), 7.54 (dd, 1H, J=8.6, 1.9 Hz), 6.82 (dd, 1H, J=8.6, 6.7 Hz)

PD 0296767

mp 249-251 °C

^{1}H-NMR (400 MHz; DMSO) δ 13.99 (broad s, 1H), 9.01 (s, 1H), 7.90 (dd, 1H, J=7.9, 2.3 Hz), 7.58 (d,1H, J=1.6 Hz), 7.42 (dd, 1H, J=8.4, 1.9 Hz), 6.69 (dd, 1H, J=8.4, 6.0 Hz), 2.24 (s, 3H)

PD 298127

mp 127-135 °C

5-chloro-N-cyclopropyl methoxy-3,4-difluoro-2-[4-iodo-2-methyl phenylamino]benzamide

^{1}H NMR (440 MHz; DMSO) δ 11.64 (s, 1H), 8.28 (s, 1H), 7.38 (dd, 1H, J=7.6, 1.7 Hz), 7.31 (d, 1 H, J=1.2 Hz), 7.15 (dd, 1H, J=8.5, 1.7 Hz), 3.35 (d, 2H, J=7.3 Hz), 2.01 (s, 3H), 0.83 (m, 1H), 0.28 (m,2H), 0.01 (m, 2H)

BIOLOGICAL ASSAYS

Example 1

Inhibition of IL-2 Production Induced by Concanavalin A (Con A)

Several of the phenyl amine MEK inhibitors described above have been evaluated in a number of assays which establish their utility in preventing the rejection of transplants in mammals. One such assay measured the ability of a test compound to inhibit the production of IL-2 from T cells (T lymphocytes) present in human peripheral blood mononuclear cells (HPBMC). In this assay, the cells (HPBMC) were prepared by first centrifuging tubes of heparinized blood (obtained from normal healthy volunteers) at 1400 rpm for 10 minutes at room temperature. The interphase containing mostly leukocytes was removed and added to a 50 mL centrifuge tube, and diluted with phosphate buffered saline (PBS) to a volume of 40 mL. The diluted PBS solution was added to a 50 mL centrifuge tube containing 7 mL of Histopague (Sigma, Sp. Gr. 1.077). The mixture was centrifuged at 2200 rpm for 20 minutes at room temperature. The middle layer, comprised mostly of peripheral blood mononuclear cells (PBMC), was removed and added to a clean 50 mL centrifuge tube. These cells were diluted with PBS to a volume of 30 mL, and centrifuged at 1000 rpm for 10 minutes at room temperature. The supernatant was removed, and the remaining cells were washed twice with 30 mL portions of PBS. The PBMC were resuspended in medium (Roswell Park Memorial Institute No. 1640 (RPMI-1640), from Gibco BRL, Gaithersburg, MD), and 10% fetal bovine serum (FBS) culture medium. The cells were adjusted to 2.5×10^6 cells/mL.

The compounds to be tested were prepared by dissolving them in dimethylsulfoxide (DMSO) to a concentration of 30 micromolar. Additional dilutions were made in RPMI-1640, and then in RPMI-1640 containing 1% DMSO so that the final in-well concentration of DMSO was 0.25% in all wells.

Concanavalin A (Con A) was purchased from CalBiochem (Catalog No. 234567). A stock solution was prepared by dissolving 250 mg of Con A in 10 mL of sterile water (25 mg/mL).

The assay was carried out by adding 50 μL of the diluted test compounds to appropriate wells of a plate. To the wells were added 100 μL of the PBMC cell solution (2.5×10^6 cells/mL). The mixtures were pre-incubated for 15 minutes at 37°C, in a 5% carbon dioxide incubator. For the HPBMC assay, 50 μL of the Con A solution (80 μg/mL Con A in RPMI-1640) were added to the appropriate wells. For the HWB assay, 50 μL of a Con A solution (800 μg/mL Con A in RPMI-1640) were added to the appropriate wells. Control wells contained medium plus 50 μL of RPMI-1640. The well plates were incubated for 2 days at 37°C in a 5% carbon dioxide incubator. At the end of Day 2, the plates were centrifuged at 2200 rpm for 5 minutes at 0-4°C. Samples of supernatant (150 μL) were removed from each well and stored at -20°C until analyzed. Each sample was analyzed by an IL-2 ELISA kit (No. D2050 from R & D Systems, Minneapolis, MN) to measure the content of IL-2.

The results of the foregoing assay are shown in Figures 1 and 9. A preferred compound to be used in accordance with this invention is 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide, also known as PD 184352. Figure 1 shows that no IL-2 is produced by unstimulated cells, but large amounts are produced in the presence of Con A. The Figure shows that PD 184352 causes a dramatic dose dependent inhibition of IL-2 production, and has an IC_{50} of 71 nM.

Figure 9 shows the inhibition of IL-2 production in cells caused by several of the phenyl amine MEK inhibitors of Formulas I and II, compared to known immunosuppressive agents dexamethasone, a steroid, which is 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione, and rolipram, a phosphodiesterase-4 inhibitor which is 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone. The data establish that the phenyl amine MEK inhibitors are in general very potent in their ability to inhibit IL-2 production.

Example 2

Inhibition of IL-2 Production Induced by Anti-CD3 & Anti-CD28

Stimulation of T cells through direct activation of the T cell receptor is felt to be more representative of physiologic T cell activation than when cells are activated by mitogens, such as Con A. The T cell receptor is a complex, multi-protein receptor comprised in part of a set up proteins collectively called CD3. In order for T cells to produce IL-2, they must also be activated by a co-receptor. The most prominent and best-characterized T cell co-receptor is CD28. Monoclonal antibodies to CD3 and CD28 and be used together to induce release of IL-2.

Anti-CD3 was purchased from BioSource Int. (catalog #AHS2812). A working solution was prepared containing 10 μg/mL of anti-CD3 in PBS. A 100 μL aliquot was added to appropriate wells and incubated for 3 hours at 37°C, and then unbound anti-CD3 was washed off with PBS. Anti-CD28 was purchased from BioSource Int. (catalog #AH0312) and was added as a solution (0.5 μg/mL) to appropriate wells after addition of HPBMC and MEK inhibitor.

HPBMC were prepared as described in Example 1 and stimulated with concentrations of anti-CD3 and anti-CD28 determined from pilot studies to provide a high degree of T cell activation, and hence IL-2 release. After a 2-day culture period in a humidified 37°C incubator containing 5% CO_2 in air, supernatant was collected and assayed for IL-2 as described in Example 1.

The results of the foregoing assay are shown in Figure 2. A preferred compound to be used in accordance with this invention is PD 184352. The Figure shows that no IL-2 is produced by unstimulated cells, but large amounts are produced in the presence of anti-3 plus anti-CD28. The Figure shows that PD 184352 causes a dramatic dose dependent inhibition of IL-2 production, and has an IC_{50} of 47 nM.

Example 3

Inhibition of Interferon-γ Production

The foregoing procedure was followed to evaluate the ability of the phenyl amine MEK inhibitors of Formulas I and II to inhibit the release of interferon gamma (IFN-gamma) from human peripheral blood mononuclear cells (HPBMC) and human whole blood (HWB). The cell samples and compound samples were prepared by the general procedure described above. The assays of the incubated well plates were carried out using an IFN-gamma ELISA kit (No. DIF00 from R & D Systems). The results of the assays are shown in Figures 3 and 10. Figure 3 shows that Con A causes a large production of IFN-gamma, and that such production is totally inhibited by PD 184352 at some concentrations. The Figure shows that the IC_{50} for PD 184352 against IFN-gamma is 148 nM.

Figure 10 shows the dose dependent inhibition of IFN-gamma caused by various phenyl amine MEK inhibitors of Formulas I and II, and the activity of known immunosuppressive agents rolipram and dexamethasone. The data establish that the phenyl amine MEK inhibitors are much more potent that rolipram, and cause almost 100% inhibition at concentrations of 1 μM or higher. The ability of the MEK inhibitors of Formulas I and II to inhibit IFN-gamma production establishes that they can be used for the prophylaxis of transplants of organs, limbs, cells, and tissues in mammals.

Example 4

Human Mixed Lymphocyte Reaction

Several of the MEK inhibitors which are to be used in the method of this invention have been evaluated in an in vitro test in which lymphocytes (or leukocytes) from one donor (eg, the potential recipient of a transplant) are cultured in the presence of leukocytes from another donor (eg, the potential transplant donor, generally a living related donor, not cadaveric donors). This test measures the degree of histoincompatibility. The assay is a mixed lymphocyte (or leukocyte) reaction, and is referred to as the "MLR". In this assay, inhibition of tritiated thymidine (^{3}H-TDR) incorporation is measured. Tritiated thymidine was supplied from Amersham (Catalog No. TRK.758, 250 μCi). The commercial

product was diluted in RPMI-1640 in a 50 mL conical centrifuge tube to provide a working stock solution of 5-10 μCi/mL. Cells and test compounds were prepared as described above. The compounds and cells were incubated at 37°C in a 5% carbon dioxide incubator. On Day 6, each well of the assay plate was labeled with the ^{3}H-TDR working stock solution (total of 0.1 - 0.5 μCi per well). The plates were incubated an additional 6 hours following labeling. The plate samples were harvested using a multichannel harvester, and the radioactivity of each sample was counted using a betaplate Wallace 1205 counter.

Figure 4 shows the activity of PD 184352 in the human MLR assay. The activity is measured as counts per minute (CPM) of tritiated thymidine (^{3}H-TDR) uptake. The Figure shows that untreated MLR values are in excess of 4500 CPM, whereas the test compound causes a dose dependent inhibition of ^{3}H-TDR uptake, with almost total inhibition occurring at 10 μM. The IC_{50} for PD 184352 was established as 186 nM.

Figure 11 shows the activity of several phenyl amine MEK inhibitors in the MLR assay, compared to dexamethasone.

The data presented in Figures 4 and 11 further establish that the selective MEK inhibitors of Formulas I and II are useful for preventing the rejection of transplanted organs, tissues, cells, and limbs in mammals.

Example 5

Inhibition of T-Cell Proliferation induced by Con A

Another measure of immunosuppressive activity is a compound's ability to block the growth of T cells. Uncontrolled proliferation of T cells leads to rejection of transplanted organs, tissues, cells, and limbs in mammals. Immunological studies have established that cyclosporine A blocks activation of T cells, and that this is partly the result of inhibition of the synthesis of interleukin-2, the main growth factor for T cells. The assay was carried out by following the general procedure described above for preparing cells and test compounds, and ^{3}H-TDR inhibition was measured. Con A was used to induce T-cell proliferation.

Figure 5 shows the degree to which PD 184352 inhibits T-cell proliferation. Namely, the compound causes about 50% inhibition of the Con A

induced proliferation at the lowest dose tested (0.12 μM), and causes almost total inhibition at the highest dose tested (10.0 μM). The IC_{50} for the compound was determined to be 340 nM.

Figure 12 shows that all of the phenyl amine MEK inhibitors that were tested caused a dramatic and dose dependent inhibition of T-cell proliferation.

Example 6

Inhibition of T-Cell Proliferation induced by Phytohemagglutinin (PHA)

The T-cell inhibition study was carried out using the agent PHA to induce the proliferation. Figure 6 shows the effects of PD 184352. In this study, the test compound failed to cause inhibition at the low dose (0.12 μM), but caused a measurable inhibition at all other doses, with almost total inhibition at the high dose (10 μM). The IC_{50} was determined to be 1.9 μM in this assay. The data further establish the ability of the phenyl amine MEK inhibitor to inhibit T-cell proliferation, and thereby to be useful in the prophylaxis of transplant rejections in mammals.

Example 7

Toxicity Assay

As noted above, the MEK inhibitors to be used in the method of this invention are potent inhibitors of transplant rejection, while at the same time have little or no toxicity, a feature which severely limits the clinical usefulness of commercial immunosuppressive agents. The toxic effects of the compounds were evaluated in an assay using MTT, which is a chemical substance known as 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide. MTT changes color when it is activated by a cell, and that color change can be measured by routine methods. Only living cells can change the color of MTT. For this assay, living U-937 cells were obtained from American Type Culture Collection (Rockville, MD). PD 184352 was added to the cells in plate wells, and the cells were incubated as described above. Following the incubation period, the color change of MTT was measured using a spectrophotometer. Figure 7 shows that PD 184352 caused no toxicity at concentrations below 33 μM, and caused only

slight color change even at concentrations as high as 100 μM. The dose of PD 184352 required to cause cell death of one-half of the cells (the TC_{50}) was thus determined to be greater than 100 μM. These data establish that the phenyl amine MEK inhibitors are essentially devoid of any toxic effects in this assay.

Figure 13 shows the toxicity of several of the phenyl amine MEK inhibitors when evaluated in the MTT assay. The data establish that all of the compounds evaluated have a very favorable therapeutic index, ie, biological efficacy for prophylaxis of transplant rejection vs toxicity. Thus, the compounds will find widespread use in the clinical setting for preventing and controlling transplant rejection in mammals.

Figure 8 shows the relative activities of several of the phenyl amine MEK inhibitors of Formulas I and II, compared with the activities of rolipram and dexamethasone, in a number of the assays described above. The Figure establishes that the phenyl amine MEK inhibitors are, in general, as active as or more active than the known agents when evaluated in standard assays which establish utility of compounds in the prophylaxis of transplant rejections in mammals.

Much of the foregoing data is summarized below in Pharmacological Table 1. The Table presents the in vitro effects of several compounds to be used in the method of this invention, together with several comparator immunosuppressive agents, on human leukocytes. The data are concentrations of test compounds required to cause a 50 percent inhibition of the measured parameter (the IC_{50}), except in the case of the toxicity data, which is presented as TC_{50} (concentration required to produce toxicity in 50 percent of the cells). In the Table, "APK" refers to activity of compounds in a cascade assay, wherein a compound inhibits a MEK enzyme, thereby preventing phosphorylation of another enzyme, namely a MAP (mitogen activated protein) kinase, which otherwise would cause phosphorylation of a substrate, in this assay said substrate being myelin basic protein The comparator agent U0126 (in Pharmacological Table 1) is 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadiene, an immunosuppressive compound described in US Patent No. 2,779,780.

PHARMACOLOGICAL TABLE 1

MEK Inhibitors: In Vitro Effects on Human Leukocytes
(All data are mean (*) IC_{50s} or % inhibition at the concentration given, except toxicity data (MTT) which are $TC_{50}S$)

	APK IC_{50} (nM)	Human IL-2 (μM)	IFN-gamma (μM)	U937 MTT TC_{50} (μM) or (% dead)	^{3}H-TDR PHA (μM)	^{3}H-TDR MLR (μM)	^{3}H-TDR Con A (μM)
171984-0000	3.0	0.019	*0.034	50.6	*2.4	0.35	*0.19
177098-0000	14.0	0.006	*0.076	*29.9	*NJ	*NJ	*3.9
177168-0000	18.0	0.052	*0.17	*13.9	*2.5	0.69	*0.52
180841-0000	4.4	*0.11	*0.21	*5.8	*ND	*NJ	*ND
184161-0000	1.6	*0.19	*0.15	*12.6	*1.8	0.53	*0.61
184352-0000	1.3	0.068	*0.14	>100 (6%)	*4.5	0.64	*0.52
184386-0000	1.4	0.039	*0.040	61	*4.0	0.41	*0.31
185625-0000	5.1	0.071	*0.12	*12.4	*NJ	*0.39	*4.0
185848-0000	1.0	0.018	*0.024	38.1	*NJ	*0.51	*NJ
188563-0000	1.3	0.013	*0.15	40	*NJ	*0.17	*NJ
198306-0000	8.0	0.037	*0.15	13.1	*1.40	*1.8	*1.9
203311-0000	--	0.032	*0.10	*32.2	*ND	*0.076	*ND

ND = not determined. NJ = no judgment: Studies indeterminant or incomplete.

PHARMACOLOGICAL TABLE 1 (cont)

MEK Inhibitors: In Vitro Effects on Human Leukocytes
(All data are mean (*) IC_{50s} or % inhibition at the concentration given, except toxicity data (MTT) which are TC_{50s})

	APK IC_{50} (nM)	Human IL-2 (μM)	IFN-gamma (μM)	U937 MTT TC_{50} (μM) or (% dead)	^{3}H-TDR PHA (μM)	^{3}H-TDR MLR (μM)	^{3}H-TDR Con A (μM)
STANDARDS							
98059-0000	>1000	*7.4	*5.8	>100 (0%)	*>10	*5.1	*>10
U0126 (PD 199601)	--	0.077	*0.25	>100 (0%)	*NJ	*0.83	*NJ
Rolipram	--	0.094	*0.65	*ND	*>10	*3.5	*NJ
Dexamethasone	--	*0.005	*0.005	>100 (0%)	*>10	*0.01	*<0.041

The foregoing extensive biological evaluations clearly establish the selective MEK inhibitors described above, especially the phenyl amines of Formulas I and II, are well-suited to the prophylaxis of transplant rejections in mammals, preferably humans. Like other immunosuppressive agents, the MEK inhibitors can be used in combination with other such agents for even better

results. For example, the MEK inhibitors can be combined clinically with agents such as cyclosporine A and FK 506, another well-known immunosuppressive agent. The agents can be combined into the same formulation, but are more typically administered in their individual formulated doses, and normally at the dose levels routinely used for the individual agents when used alone; however, lower or higher doses can be used if desired. The individual agents can be packaged together for convenience of the medical practitioner, for example in a kit or the like.

Example 8

The selective MEK inhibitors to be used in the method of this invention will additionally be evaluated in in vivo assays that establish their ability to prevent and control transplant rejections. A typical in vivo assay is an allogeneic mouse ear-heart model using neonatal or newborn mouse hearts. Mice of the BL/6 to C3H strain will be used as test animals. Ten mice will be treated with a MEK inhibitor. Three vehicle control allografts will be included, as well as three isografts, as control animals. Mice will be dosed at 50 mg/kg twice each day, until grafts are rejected, or until there is evidence of a definite anti-rejection effect. The MEK inhibitor being evaluated will be dissolved in a dosing solution which is 10% ethanol, 10% Cremophor EL (Sigma, Cat. No. C-5135), and 80% water (v/v/v). The test animals are dosed orally using a tuberculin syringe and a mouse oral gavage tube. The dosing ratio is 0.1 mL of solution per each 20 g of mouse weight. The MEK inhibitor (300 mg) to be tested is placed in a 50 mL conical tube, and 3.0 mL of ethanol is added. The tube is capped to retard evaporation and vortexed to facilitate dissolution. The Cremophor EL (3.0 mL) is added, followed by the addition of 24.0 mL of water. The 30 mL dosing solution is vortexed, and stored at 5°C until used.

If any grafts are rejected at any time during the study, the animal is sacrificed by dry ice (CO_2) asphyxiation as soon as graft rejection is determined. All specimens are obtained immediately after sacrificing the animals, and placed in 10-20 mL of buffered formalin. If all allografts survive to the end of the study, one-half are placed in the buffered formalin, and the other half are frozen for subsequent analysis. The following tissues are collected for histopathology and

phospho-ERK analysis: ear bearing the allograft (or isograft); ipsilateral cervical lymph nodes; contralateral cervical lymph nodes; the spleen; and heparinized blood collected by cardiac puncture for determination of drug concentration. If transplants are still surviving on Day 50, the study is terminated, and the above noted specimens are collected and analyzed.

The method of this invention provides for both prophylaxis and maintenance of patients who have undergone a transplant or are scheduled to undergo a transplant. Evaluation of one MEK inhibitor, 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide (PD 198306)) was performed using the aforementioned protocol, but no enhancement of graft survival was observed (data not shown). This may be the result of any or a combination of several factors, among which is insufficient exposure of target cells to an adequate and sustained concentration of the MEK inhibitor. Survival time of isografts in mice treated with PD 198306 was somewhat shortened, which may suggest that MEK inhibitors might be more efficacious for graft maintenance.

D. Other Embodiments

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

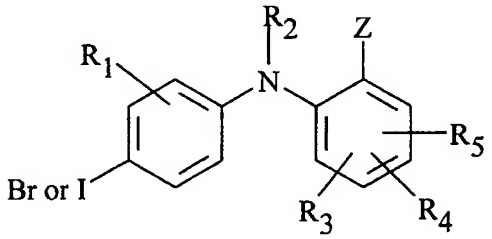
CLAIMS

1. A method for preventing and controlling the rejection, in a patient, of a transplanted organ, cell, tissue, or limb, said method comprising administering to the patient who has undergone a transplant, or who is scheduled to undergo a transplant, an effective immunosuppressive amount of a MEK inhibitor.

2. A method according to Claim 1 wherein the MEK inhibitor administered is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran.

3. The method according to Claim 1, wherein said MEK inhibitor is a selective MEK 1 or MEK 2 inhibitor.

4. The method according to Claim 1 wherein the MEK inhibitor is a compound of Formula I



I

wherein:

R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_2 is hydrogen;

R_3, R_4, and R_5 independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or -(O or NH)$_m$-$(CH_2)_n$-R_9, where R_9 is hydrogen, hydroxy, COOH, or $NR_{10}R_{11}$;

n is 0-4;

m is 0 or 1;

R_{10} and R_{11} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7;

R_6 and R_7 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, (CO)-C_1-C_8 alkyl, aryl, heteroaryl, C_3-C_{10} cycloalkyl, or C_3-C_{10} (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R_6 and R_7 together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl; and wherein any of the foregoing alkyl, alkenyl, aryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl,phenoxy, C_3-C_5 heteroaryl, or C_3-C_5 heteroaryloxy;

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

5. The method according to Claim 4 wherein the MEK inhibitor is a compound selected from:

[4-Chloro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine;

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine;

[4-nitro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine;

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;

4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;

5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;

2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide;

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide;

5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanone;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;

N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone;

5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;

N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol;

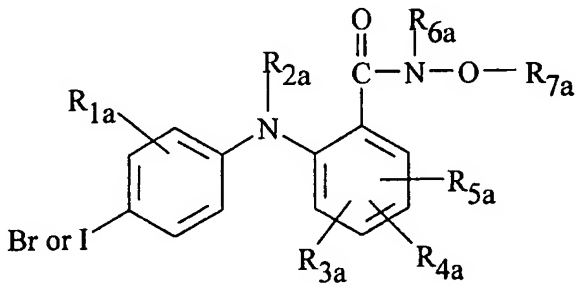
[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol; and

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

6. The method of claim 4, wherein the MEK inhibitor is a compound of Formula (I) wherein (a) R_1 is hydrogen, methyl, methoxy, fluoro, chloro, or bromo; (b) R_2 is hydrogen; (c) R_3, R_4, and R_5 independently are hydrogen, fluoro, chloro, bromo, iodo, methyl, methoxy, or nitro; (d) R_{10} and R_{11} independently are hydrogen or methyl; (e) Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7; R_6 and R_7 independently are hydrogen, C $_{1-4}$ alkyl, heteroaryl, or C $_{3-5}$ cycloalkyl optionally containing one or two heteroatoms selected from O, S, or NH; or R_6 and R_7 together with the nitrogen to which they are attached complete a 5-6 member cyclic ring optionally containing 1 or 2 additional heteroatoms selected from O, NH or N-alkyl; and wherein any of the foregoing alkyl or aryl groups can be unsubstituted or substituted by halo, hydroxy, methoxy, ethoxy, or heteroaryloxy; (f) Z is $COOR_7$; (g) R7 is H, pentafluorophenyl, or tetrazolyl; (h) R_3, R_4, and R_5 are independently H, fluoro, or chloro; (i) R_4 is fluoro; (j) two of R_3, R_4, and R_5 are fluoro; or (k) combinations of the above.

7. The method of claim 6, wherein the MEK inhibitor is a compound of Formula (I) wherein: Z is $COOR_7$; R_7 is H, pentafluorophenyl, or tetrazolyl; R_3 and R_5 are independently H, fluoro, or chloro; and R_4 is fluoro.

8. A method according to claim 1, where the MEK inhibitor is a compound of Formula II



II

wherein:

R_{1a} is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_{2a} is hydrogen;

R_{3a}, R_{4a}, and R_{5a} independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or $(O \text{ or } NH)_m$-$(CH_2)_n$-R_{9a}, where R_{9a} is hydrogen, hydroxy, CO_2H or $NR_{10a}R_{11a}$.

n is 0-4;

m is 0 or 1;

R_{10a} and R_{11a} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

R_{6a} is hydrogen, C_1-C_8 alkyl, (CO)-C_1-C_8 alkyl, aryl, aralkyl, or C_3-C_{10} cycloalkyl;

R_{7a} is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{10} (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a});

and wherein any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl, phenoxy, C_3-C_5 heteroaryl or heterocyclic radical, or C_3-C_5 heteroaryloxy or heterocyclic radical-oxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or $NR_{10a}R_{11a}$;

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

9. The method of Claim 8, comprising a MEK inhibitor having a structure of Formula (II) wherein: (a) R_{1a} is H, methyl, fluoro, or chloro; (b) R_{2a} is H; R_{3a}, R_{4a}, and R_{5a} are each H, Cl, nitro, or F; (c) R_{6a} is H; (d) R_{7a} is methyl, ethyl, 2-propenyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclobutyl methyl, cyclopropylmethyl, or cyclopropylethyl; and (e) the 4' position is I, rather than Br.

10. The method of claim 9, comprising a MEK inhibitor having a structure of Formula (II) wherein: R_{4a} is F at the 4 position, para to the CO-N-R_{6a}-OR_{7a} group and meta to the bridging nitrogen; at least one of R_{3a} and R_{5a} is F or Cl; and R_{1a} is methyl or chloro.

11. The method of Claim 8, comprising a MEK inhibitor having a formula selected from:

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide;

5-Bromo-3-4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-ynyloxy)-benzamide;

5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide;

4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methyl-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide;

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide; and

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide.

12. The method of claim 1, comprising a MEK inhibitor having a structure selected from:

2-(2-chloro-4-iodophenylamino)-5-chloro-N-cyclopropylmethoxy -3,4-difluorobenzamide (PD 297189); 2-(4-iodophenylamino)-N-cyclopropylmethoxy-5-chloro-3,4-difluorobenzamide (PD 297190); 2-(4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296771); 2-(2-chloro-4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296770); 5-chloro-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid (PD 296767); and 5-chloro-N-cyclopropylmethoxy -3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide (PD 298127).

13. A method for preventing and controlling the rejection in a patient of a transplanted organ, cell, tissue or limb, said method comprising the step of administering to the patient who has undergone a transplant, or who is scheduled to undergo a transplant, an effective immunosuppressive amount of a compound selected from:

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD184352);

2-(2-Methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD170611);

2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD171984);

2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD177168);

2-(2-Methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-5-bromobenzamide (PD 180841);

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 184161);

2-(2-Chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD184386);

2-(2-Chloro-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluorobenzamide (PD 185625);

2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD 185848);

2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluorobenzamide(PD 188563);

2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide (PD 198306); and

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide (PD 203311).

14. A method for the prophylaxis or maintenance of transplant rejection in a mammal comprising administering to a patient in need of prophylaxis or maintenance an effective amount of 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide.

15. A method for the prophylaxis or maintenance of transplant rejection in a mammal comprising administering to a patient in need of prophylaxis or maintenance an effective amount of 2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide.

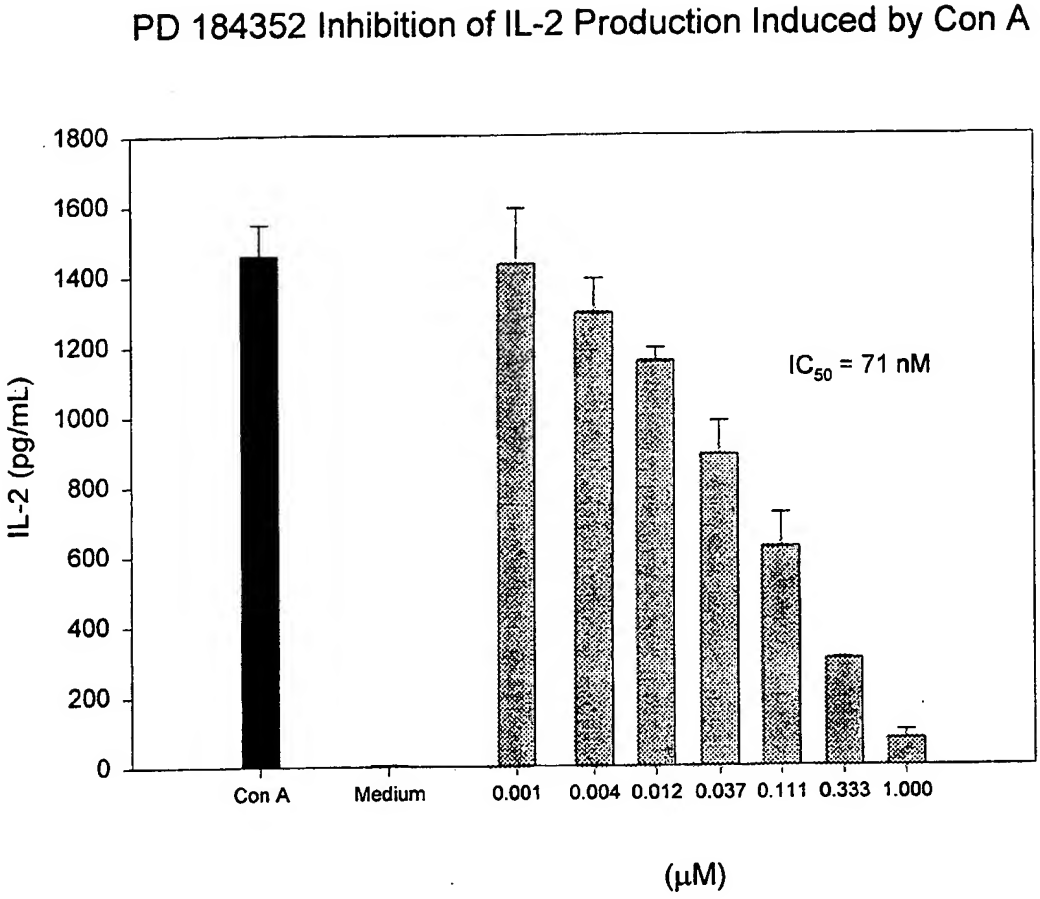

PD 184352 Inhibition of IL-2 Production Induced by Con A
IL-2 (pg/mL)
1800
1600
1400
1200
1000
800
600
400
200
0
IC50 = 71 nM
Con A
Medium
0.001
0.004
0.012
0.037
0.111
0.333
1.000
(μM)

Figure 1

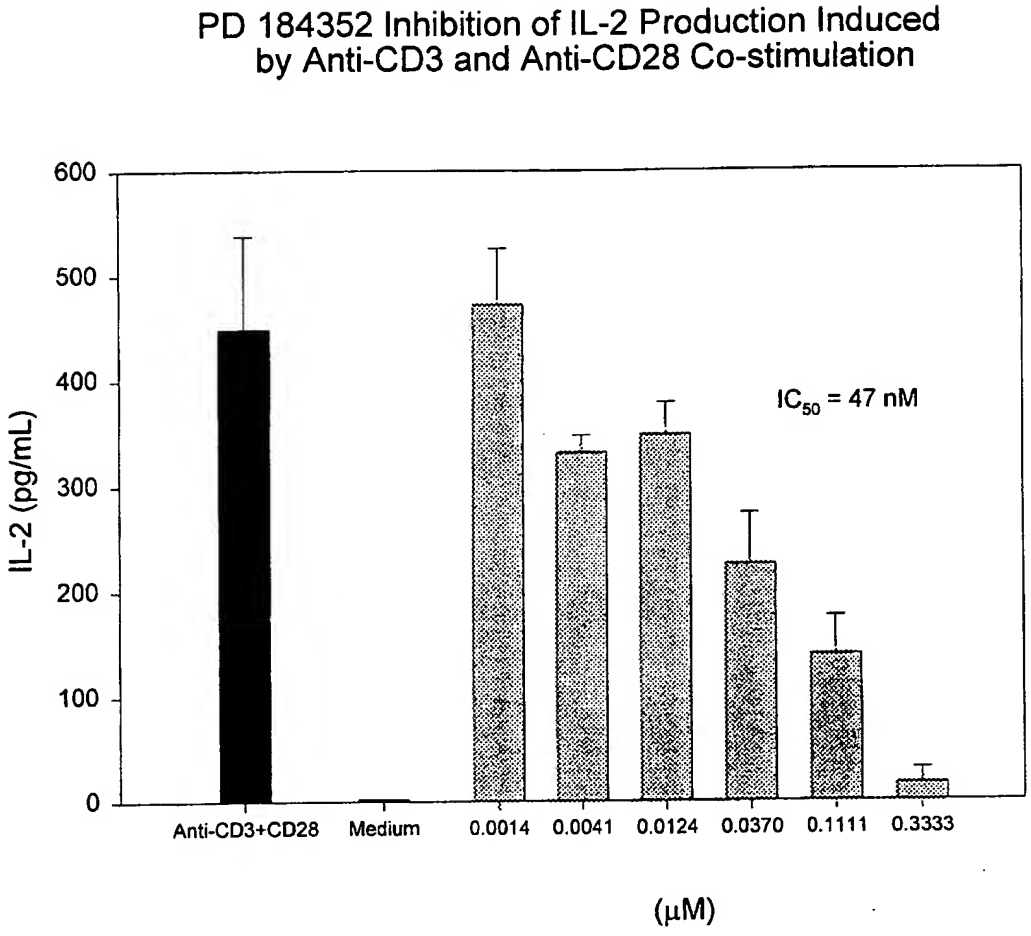

PD 184352 Inhibition of IL-2 Production Induced by Anti-CD3 and Anti-CD28 Co-stimulation
IL-2 (pg/mL)
600
500
400
300
200
100
0
IC50 = 47 nM
Anti-CD3+CD28
Medium
0.0014
0.0041
0.0124
0.0370
0.1111
0.3333
(μM)

Figure 2

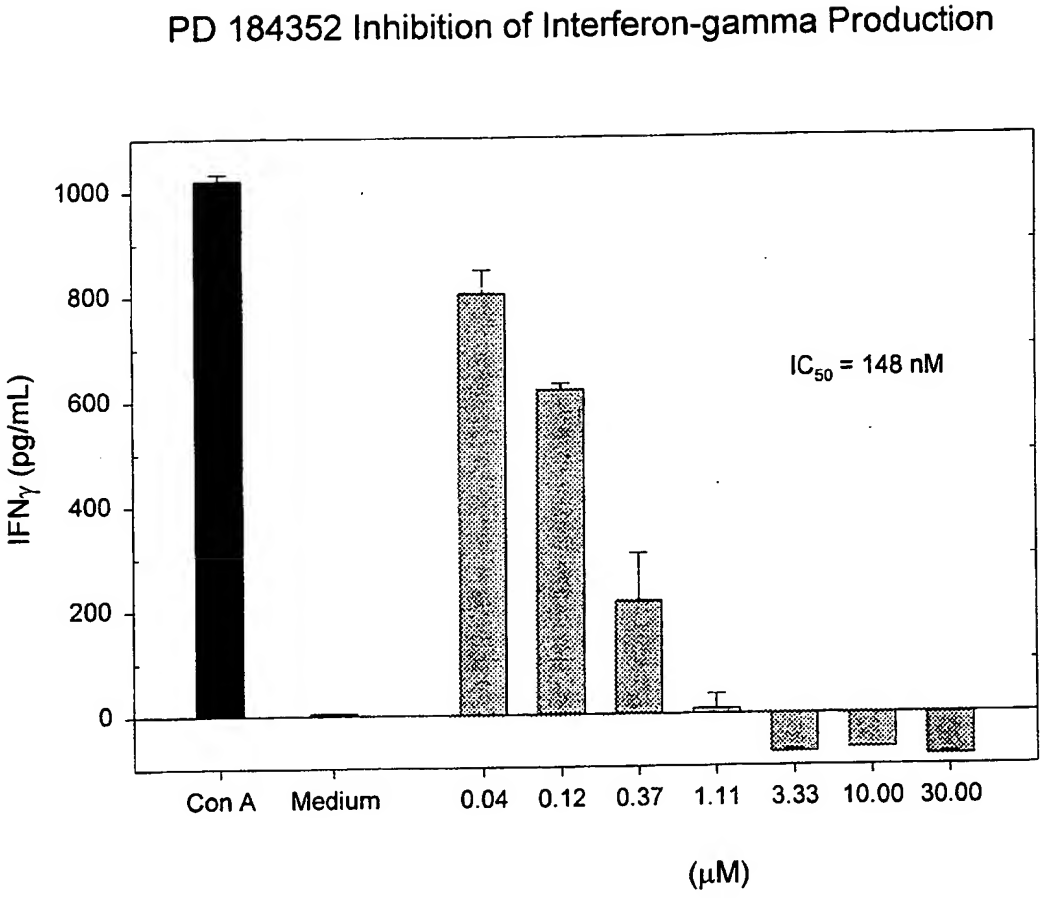

PD 184352 Inhibition of Interferon-gamma Production
IFNγ (pg/mL)
1000
800
600
400
200
0
IC50 = 148 nM
Con A
Medium
0.04
0.12
0.37
1.11
3.33
10.00
30.00
(μM)

Figure 3

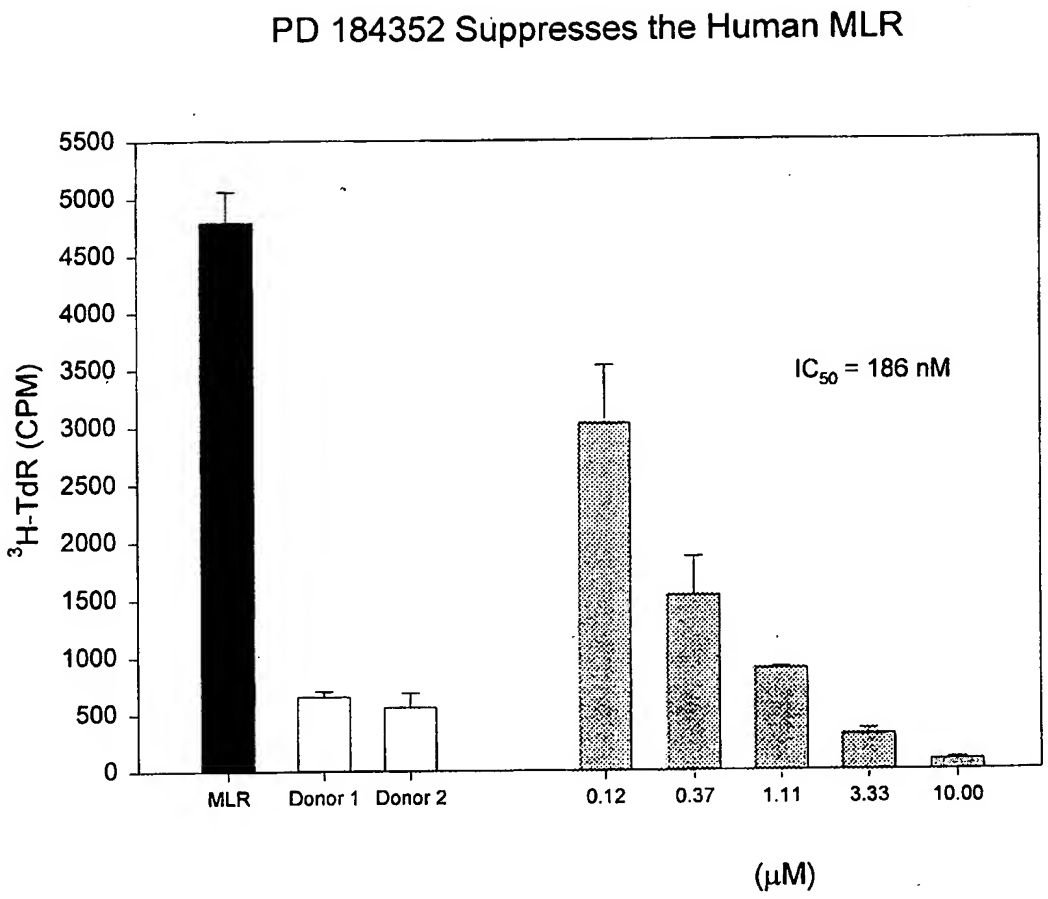

PD 184352 Suppresses the Human MLR
^{3}H-TdR (CPM)
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
IC$_{50}$ = 186 nM
MLR
Donor 1
Donor 2
0.12
0.37
1.11
3.33
10.00
(μM)

Figure 4

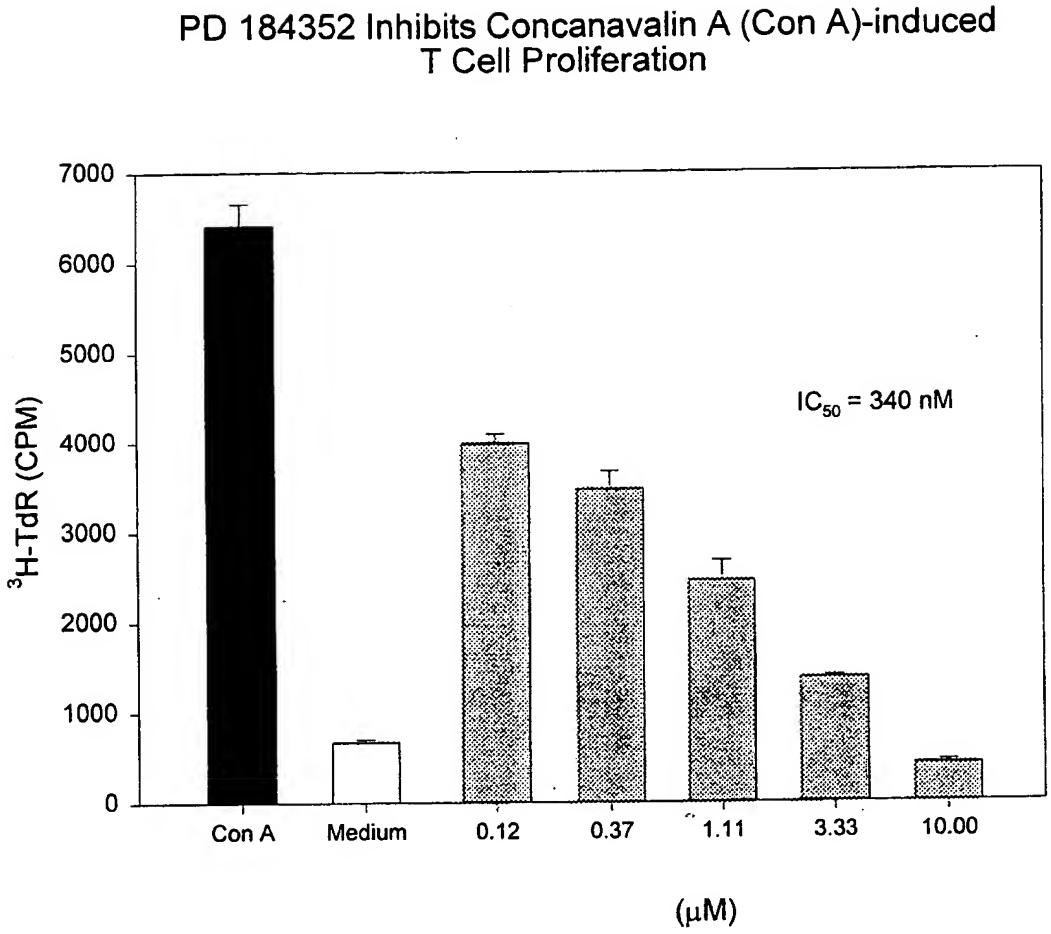

PD 184352 Inhibits Concanavalin A (Con A)-induced T Cell Proliferation
7000
6000
5000
4000
3000
2000
1000
0
^{3}H-TdR (CPM)
IC_{50} = 340 nM
Con A
Medium
0.12
0.37
1.11
3.33
10.00
(μM)

Figure 5

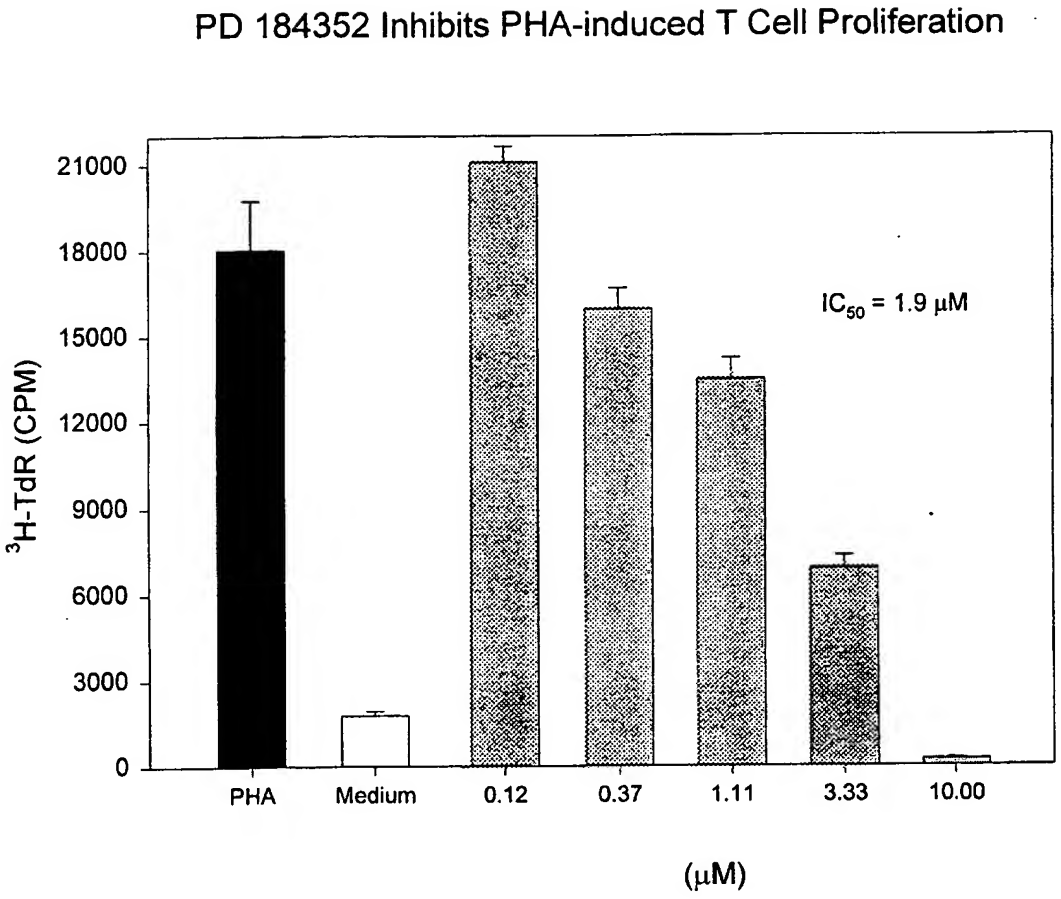

PD 184352 Inhibits PHA-induced T Cell Proliferation
^{3}H-TdR (CPM)
21000
18000
15000
12000
9000
6000
3000
0
IC_{50} = 1.9 µM
PHA
Medium
0.12
0.37
1.11
3.33
10.00
(µM)

Figure 6

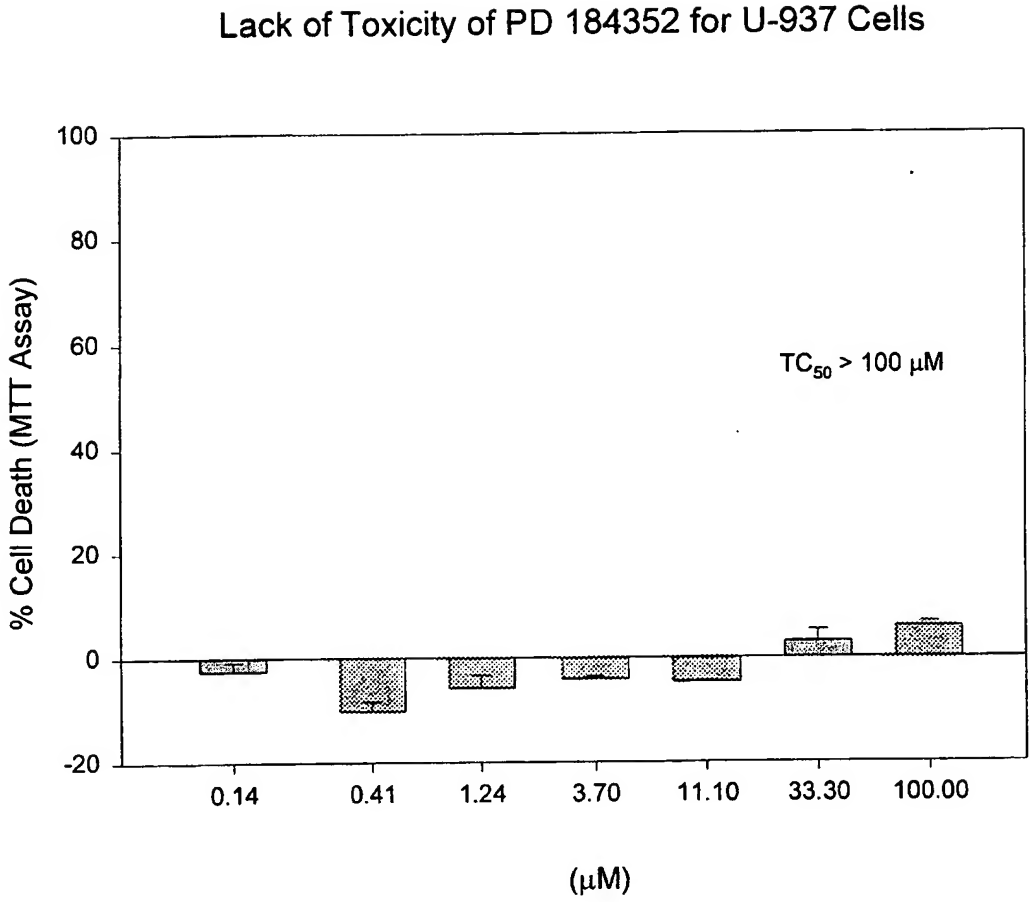
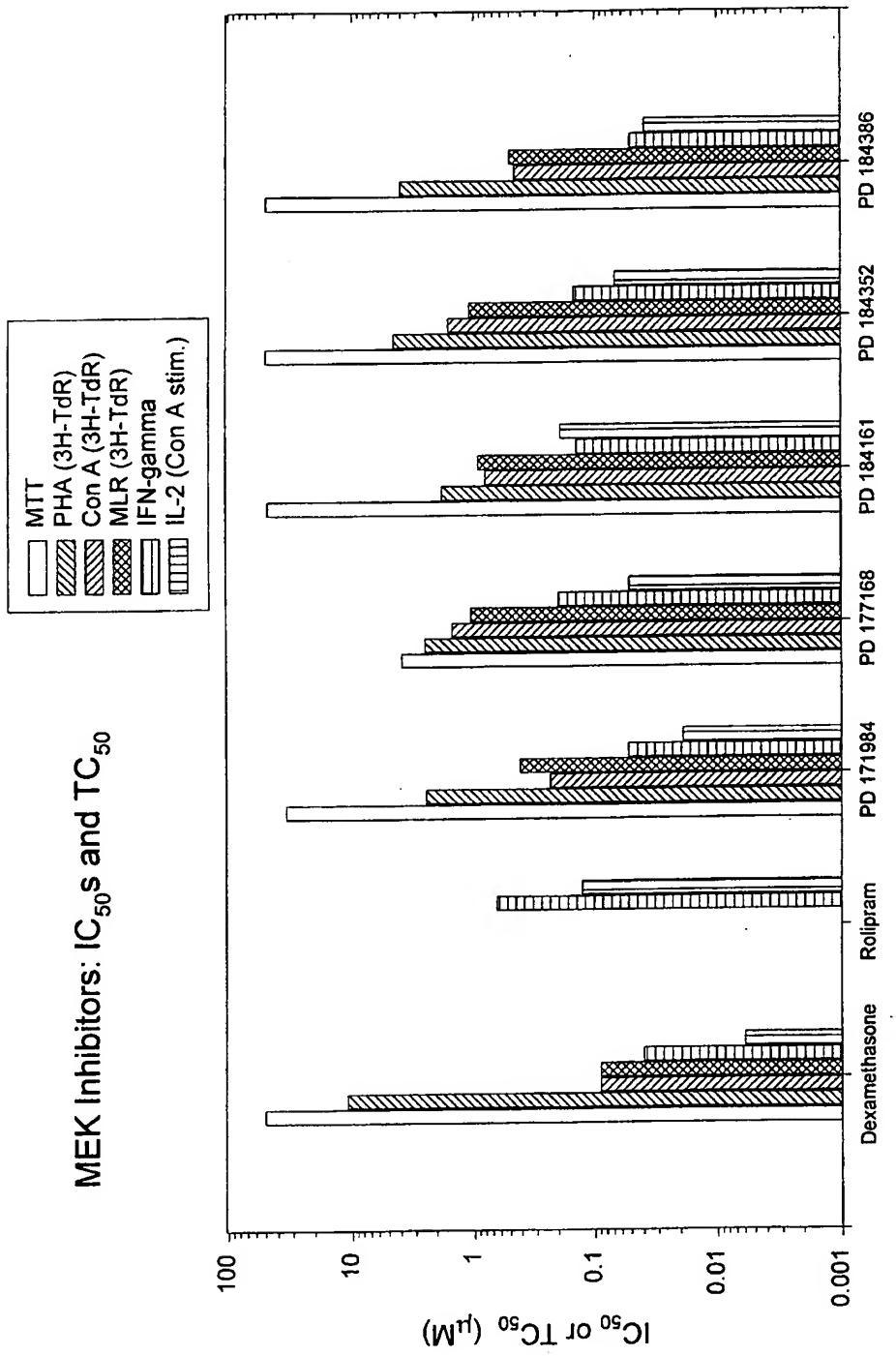

Lack of Toxicity of PD 184352 for U-937 Cells
100
80
60
40
20
0
-20
% Cell Death (MTT Assay)
TC50 > 100 µM
0.14
0.41
1.24
3.70
11.10
33.30
100.00
(µM)

Figure 7

Figure 8


MEK Inhibitors: IC50s and TC50
MTT
PHA (3H-TdR)
Con A (3H-TdR)
MLR (3H-TdR)
IFN-gamma
IL-2 (Con A stim.)
IC50 or TC50 (μM)
100
10
1
0.1
0.01
0.001
Dexamethasone
Rolipram
PD 171984
PD 177168
PD 184161
PD 184352
PD 184386

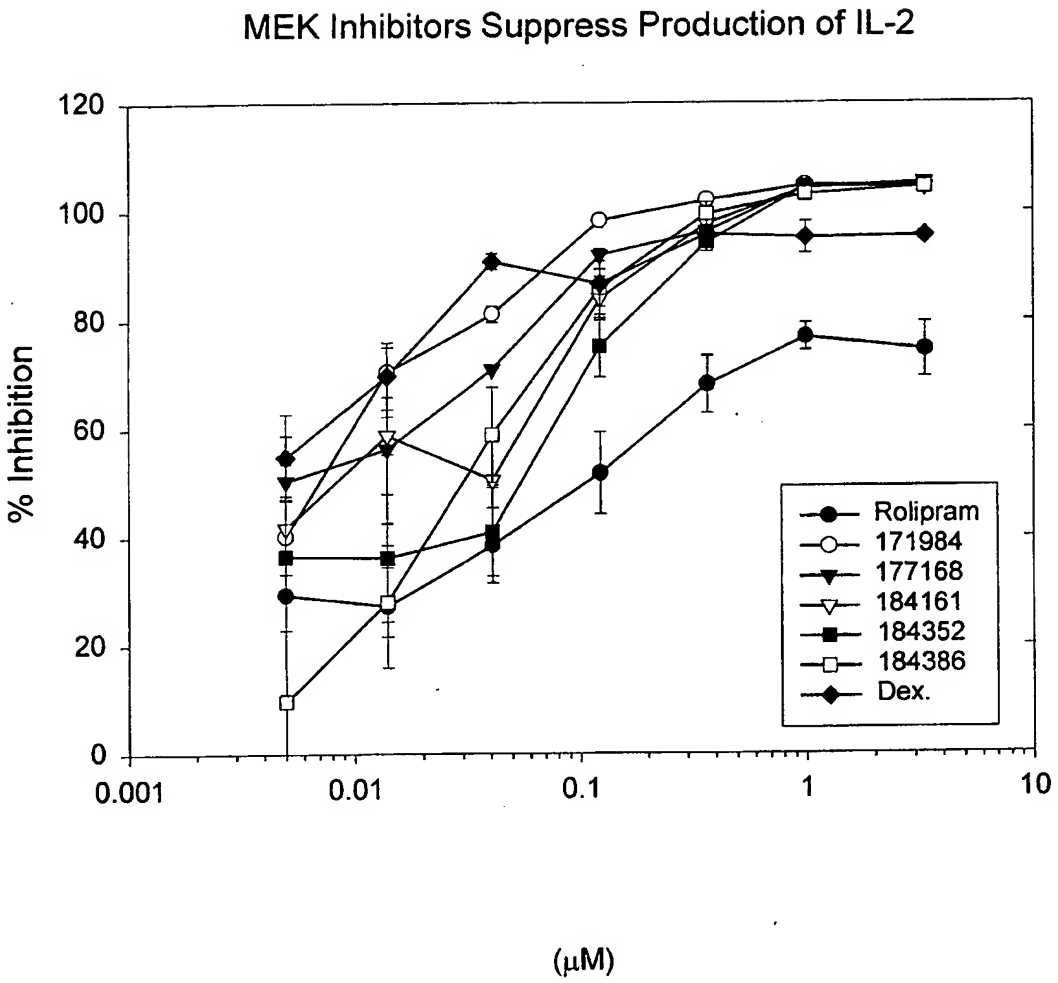

MEK Inhibitors Suppress Production of IL-2
% Inhibition
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
(μM)
Rolipram
171984
177168
184161
184352
184386
Dex.

Figure 9

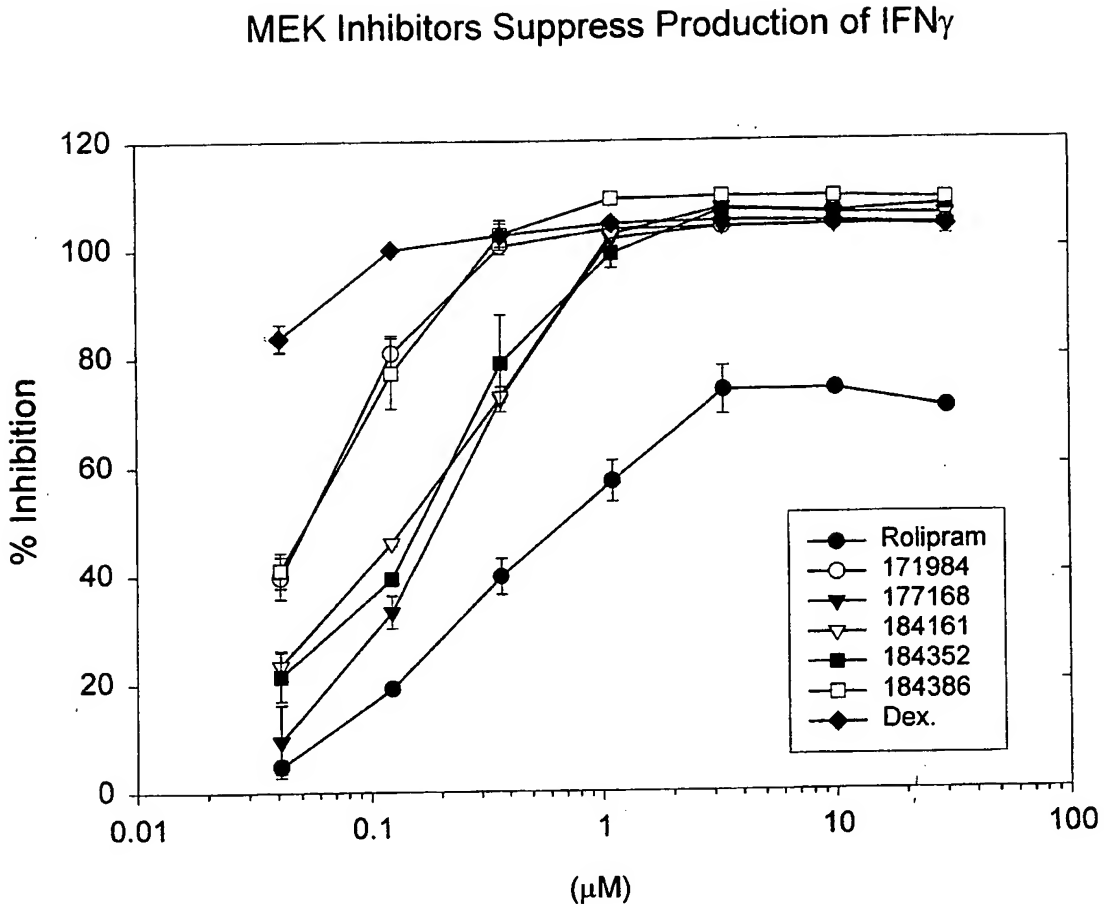

MEK Inhibitors Suppress Production of IFNγ
% Inhibition
120
100
80
60
40
20
0
0.01
0.1
1
10
100
(μM)
Rolipram
171984
177168
184161
184352
184386
Dex.

Figure 10

MEK Inhibitors Suppress the Human MLR

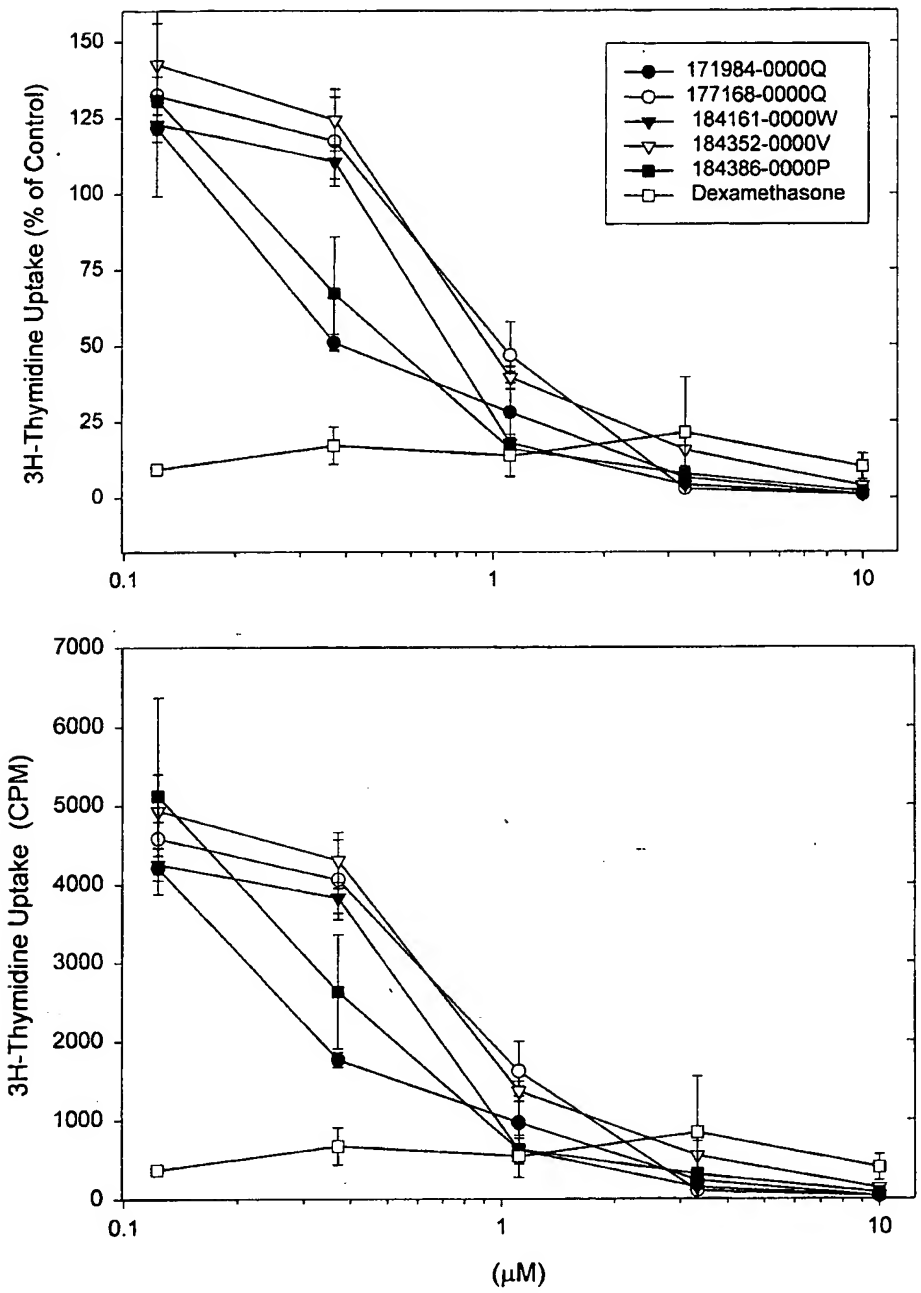


Figure 11

MEK Inhibitors Suppress Human T Cell Proliferation

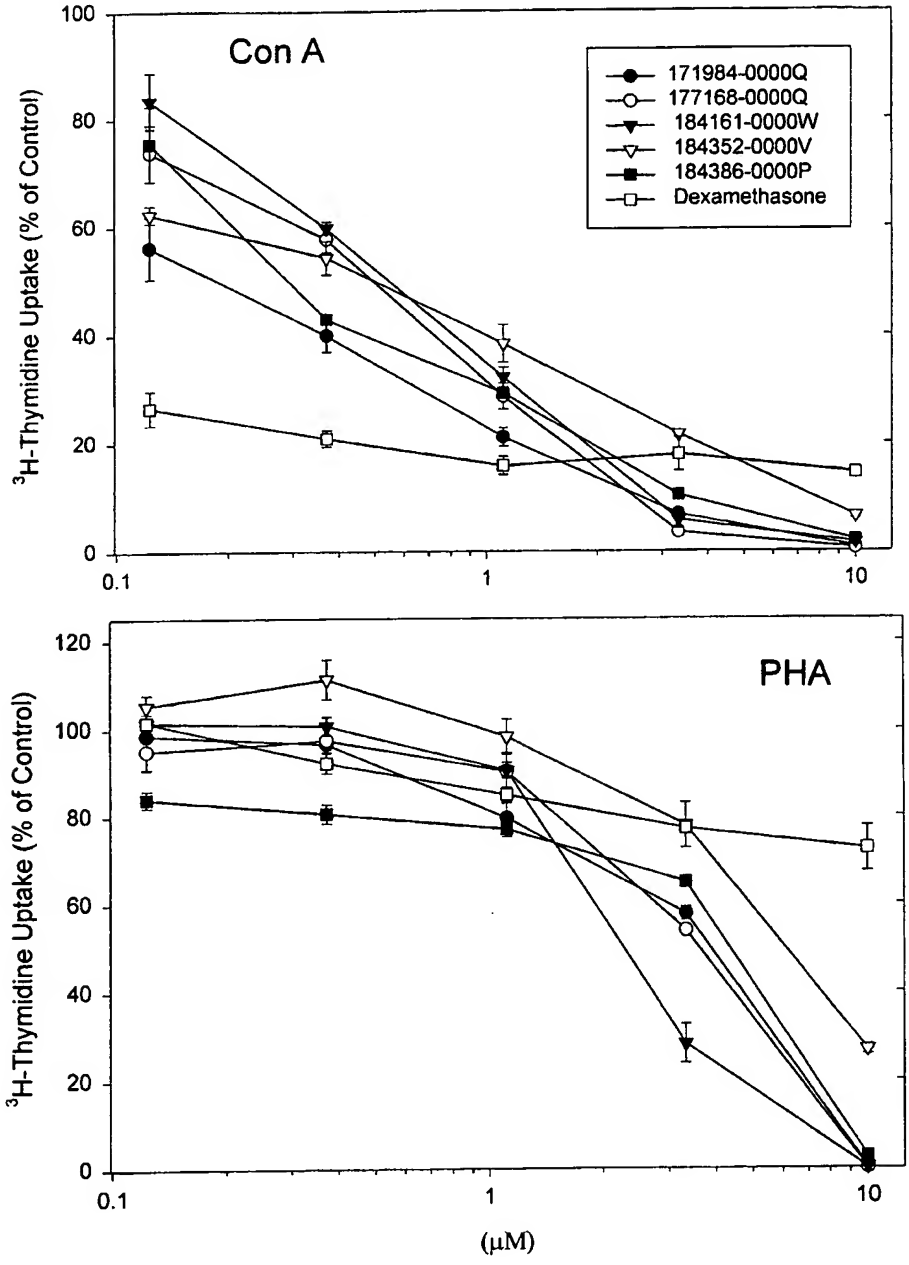


Figure 12

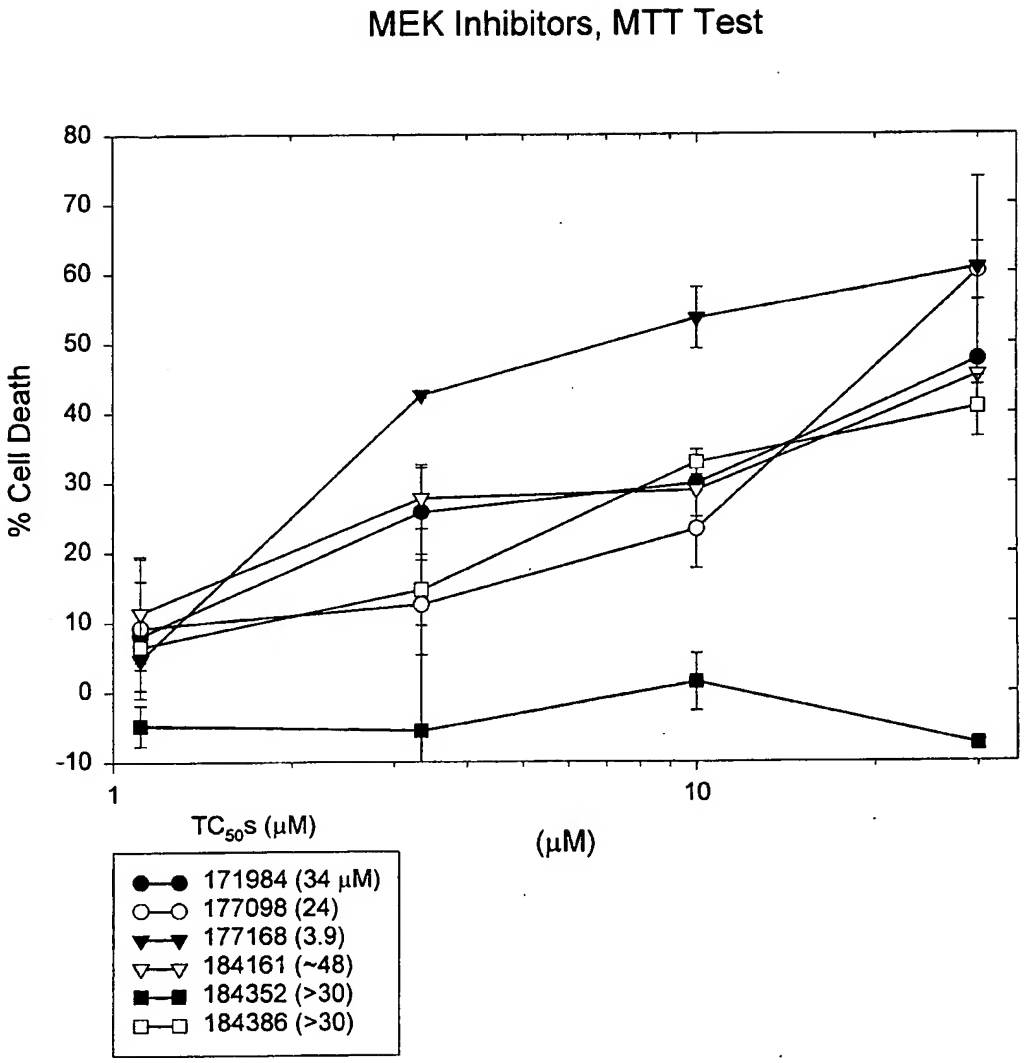

MEK Inhibitors, MTT Test
% Cell Death
80
70
60
50
40
30
20
10
0
-10
1
10
(μM)
TC50s (μM)
171984 (34 μM)
177098 (24)
177168 (3.9)
184161 (~48)
184352 (>30)
184386 (>30)

Figure 13

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/29591

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/196 A61K31/166 A61K31/136 A61K31/41
A61K31/495 A61K31/4453 A61K31/40 A61K31/4465 A61K31/5375
A61K31/381 A61K31/341 A61K31/18 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 34792 A (GEN HOSPITAL CORP) 15 July 1999 (1999-07-15) abstract page 2, line 1 -page 3, line 2 page 4, line 7 - line 21 page 14, line 2 - line 6; claims	1-3
X	WO 96 31206 A (WARNER LAMBERT CO) 10 October 1996 (1996-10-10) abstract page 3, line 10 - line 28 page 17, line 10 page 29, line 9 - line 15; claims page 39, line 26	1-3

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hoff, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/29591

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 22985 A (WARNER LAMBERT CO) 1 August 1996 (1996-08-01) cited in the application the whole document	1-3
X	WO 96 01111 A (WILLIAMS JAMES W) 18 January 1996 (1996-01-18) the whole document	1,3
P,A	MANNA S K ET AL: "Immunosuppressive leflunomide metabolite (A77 1726) blocks TNF-dependent nuclear factor-kappa B activation and gene expression." JOURNAL OF IMMUNOLOGY, (1999 FEB 15) 162 (4) 2095-102. , XP000907249 page 2100, right-hand column, paragraph 1 figure 7	1,3
Y	EP 0 316 630 A (WARNER LAMBERT CO) 24 May 1989 (1989-05-24) abstract page 8, line 51 - line 52 claims; examples 14,19	1,3,8,11
Y	WO 98 37881 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 3 September 1998 (1998-09-03) cited in the application abstract; claims; examples	1,3,8,11
P,A	WO 99 01426 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) the whole document	1-15
P,A	WO 99 01421 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) the whole document	1-15

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/29591

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 29591

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,3 relate to a compound defined by reference to its pharmacological property, namely "MEK inhibitor".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Furthermore, present claims 4 and 8 relate to an extremely large number of possible compounds, namely any esters, amides or prodrugs of the compounds of formulae I and II. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds structurally identified in claims 2,4-15 and to their pharmaceutically acceptable salts, with due regard to the general idea underlying the present invention.

Claims searched completely: 2,5-7,9-15
Claims searched incompletely: 1,3,4,8

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ional Application No
PCT/US 99/29591

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9934792 A	15-07-1999	AU 1951499 A	26-07-1999
WO 9631206 A	10-10-1996	AU 5259296 A	23-10-1996
WO 9622985 A	01-08-1996	US 5525625 A	11-06-1996
		AT 181913 T	15-07-1999
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		DE 69510696 D	12-08-1999
		DE 69510696 T	23-12-1999
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		AU 2954195 A	25-01-1996
		US 5688824 A	18-11-1997
EP 0316630 A	24-05-1989	US 5155110 A	13-10-1992
		AU 2909289 A	23-05-1989
		WO 8903818 A	05-05-1989
		ZA 8807696 A	27-06-1990
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		ZA 9801578 A	02-09-1998
WO 9901426 A	14-01-1999	AU 8262798 A	25-01-1999
		EP 0993439 A	19-04-2000
		HR 980368 A	30-04-1999
		NO 996491 A	29-12-1999
		ZA 9805728 A	27-01-1999
WO 9901421 A	14-01-1999	AU 8262698 A	25-01-1999
		EP 0993437 A	19-04-2000
		HR 980369 A	30-04-1999
		ZA 9805726 A	27-01-1999

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 June 2000 (22.06.2000)

PCT

(10) International Publication Number
WO 00/35435 A1

(51) International Patent Classification[7]: A61K 31/00, 31/196, 31/166, 31/136, 31/41, 31/495, 31/4453, 31/40, 31/4465, 31/5375, 31/381, 31/341, 31/18, A61P 37/06

(21) International Application Number: PCT/US99/29591

(22) International Filing Date:
14 December 1999 (14.12.1999)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/112,369 15 December 1998 (15.12.1998) US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

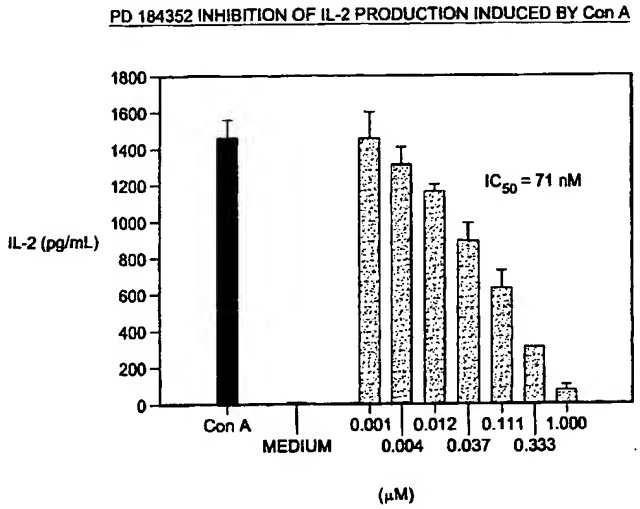
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: GILBERTSEN, Richard, Buell [US/US]; 3600 Deerfield Place, Ann Arbor, MI 48103 (US).

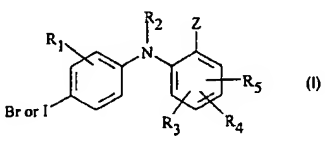
(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

(81) Designated States *(national)*: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

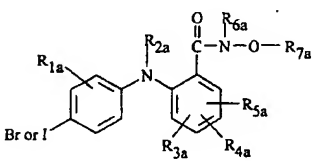
[Continued on next page]

(54) Title: USE OF A MEK INHIBITOR FOR PREVENTING TRANSPLANT REJECTION





(I)



(II)

(57) Abstract: This invention provides a method for the prophylaxis or maintenance of rejection of transplants of organs, cells, limbs, and tissues in mammals, comprising administering a selective MEK inhibitor, preferably a compound of formulas (I) and (II).

WO 00/35435 A1

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(48) **Date of publication of this corrected version:**
22 March 2001

(15) **Information about Correction:**
see PCT Gazette No. 12/2001 of 22 March 2001, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

USE OF A MEK INHIBITOR FOR PREVENTING TRANSPLANT REJECTION

FIELD OF THE INVENTION

This invention relates to a method for preventing mammals that have undergone an organ, tissue, cell, or limb transplant from rejecting the transplant. The method comprises administering an effective amount of a MEK inhibitor, ideally a phenyl amine derivative.

BACKGROUND OF THE INVENTION

Transplantation of organs and limbs has become a common procedure to treat mammals that have diseased organs, or have been the victims of accidents or other traumas that have resulted in loss of organ function or limbs. Routinely transplanted organs include the liver, kidney, pancreas, and lung. Other types of transplantation are also common, such as skin, bone marrow, and small intestine. Limb transplantation includes fingers, toes, and larger limbs such as arms.

Transplant rejection involves both humoral immunity and a cell-mediated immune reaction, or a delayed type hypersensitivity response in a mammal patient. As a result, the patient receives an immunosuppressant agent to control or at least diminish the rejection response. While several immunosuppressants are currently available for clinical use, each is associated with adverse side effects. For example, cyclosporine is a cyclic peptide which inhibits the T-cell production of several cytokines, including IL-2 (interleukin-2), IL-3, IL-4, IL-5, IFN-δ, and probably other lymphokines. Cyclosporine is used extensively for the prophylaxis of organ rejection in allogeneic kidney, liver, and heart transplants. Cyclosporine is often used in combination with other immunosuppressant agents such as corticosteroids or azathioprine. Unfortunate side effects associated with cyclosporine include nephrotoxicity, hepatotoxicity, severe renal dysfunction, tremor, hirsutism, and hypertension.

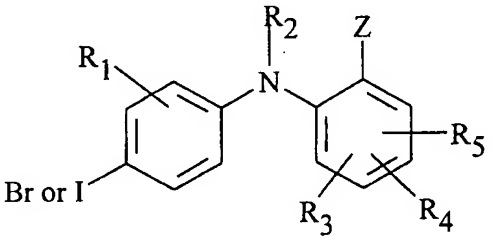
Another immunosuppressive agent is mycophenolate mofetil, the 2-morpholinoethyl ester of mycophenolic acid that is frequently used by patients

receiving allogeneic renal transplants. This agent is often used in combination with other immunosuppressive agents, including cyclosporine and corticosteroids. Like cyclosporine, mycophenolate mofetil can cause side effects, most notably the increased risk of developing lymphomas and other malignancies, particularly concerning the skin. Adverse effects on fetal development have also been noted.

In view of the above, there is a continuing need for immunosuppressant agents not only useful for treating or preventing transplant rejection but also with less severe side effects than those associated with existing therapy. According to the present invention, compounds that are MEK inhibitors are useful for preventing rejection of transplants in mammals. Moreover, these potent immunosuppressive agents may have fewer or no adverse side effects. The compounds to be administered according to this invention are described in US Patent No. 5,525,625, and in WO 98/37881, both of which are incorporated herein by reference.

SUMMARY OF THE INVENTION

This invention provides a method for the prevention of rejection in a mammal of transplanted organs, tissues, and limbs, said method including administering an effective immunosuppressive amount of a selective MEK inhibitor to a subject who has undergone a transplant or is scheduled to undergo a transplant. In a preferred embodiment, the MEK inhibitor administered is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran, also known as "98059", as described in US 5,525,625. In another preferred embodiment, the immunosuppressive agent administered is a phenyl amine compound of Formula I or II:



I

In formula (I), R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN. R_2 is hydrogen. R_3, R_4, and R_5 are independently selected from hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, and -(O or NH)$_m$-$(CH_2)_n$-R_9. R_9 is hydrogen, hydroxy, COOH, or $NR_{10}R_{11}$; n is 0-4; m is 0 or 1. Each of R_{10} and R_{11} is independently selected from hydrogen and C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-(C_1-C_8 alkyl). Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7. R_6 and R_7 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, (CO)-C_1-C_8 alkyl, aryl, heteroaryl, C_3-C_{10} cycloalkyl, or C_3-C_{10} (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R_6 and R_7 together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl. In formula (I), any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl, phenoxy, C_3-C_5 heteroaryl, or C_3-C_5 heteroaryloxy; or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

Preferred embodiments of Formula (I) have a structure wherein: (a) R_1 is hydrogen, methyl, methoxy, fluoro, chloro, or bromo; (b) R_2 is hydrogen; (c) R_3, R_4, and R_5 independently are hydrogen, fluoro, chloro, bromo, iodo, methyl, methoxy, or nitro; (d) R_{10} and R_{11} independently are hydrogen or methyl; (e) Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7; R_6 and R_7 independently are hydrogen, C_{1-4} alkyl, heteroaryl, or C_{3-5} cycloalkyl optionally containing one or two heteroatoms selected from O, S, or NH; or R_6 and R_7 together with the nitrogen to which they are attached complete a 5-6 member cyclic ring optionally containing 1 or 2 additional heteroatoms selected from O, NH or N-alkyl; and wherein any of the foregoing alkyl or aryl groups can be unsubstituted or substituted by halo, hydroxy, methoxy, ethoxy, or heteroaryloxy

(such as the synthetic intermediate 2,3,4,5,6-pentafluorophenyl); (f) Z is $COOR_7$; (g) R_7 is H, pentafluorophenyl, or tetrazolyl; (h) R_3, R_4, and R_5 are independently H, fluoro, or chloro; (i) R_4 is fluoro; (j) two of R_3, R_4, and R_5 are fluoro; or (k) combinations of the above. In another preferred embodiment of Formula (I), R_1 is methyl, fluoro, chloro, or bromo.

Examples of preferred embodiments include methods comprising a MEK inhibitor selected from Formula (I) Compound Table below.

FORMULA (I) COMPOUND TABLE
(page 1 of 10)

[4-Chloro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine

[4-nitro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine

4-Fluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid

4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-2-methyl-phenylamino)-benzoic acid

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid

5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid

2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid

2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 2 of 10)

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide
5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide
N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide
N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide
5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide
3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 3 of 10)

4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide
N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide
3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide
4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 4 of 10)

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)-benzamide

5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 5 of 10)

5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide
5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide
(3-Hydroxy-pyrrolidin-1-yl)-[5-nitro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanone
5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl-phenylamino)- benzamide
N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl-phenylamino)- benzamide
N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide
5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide
5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 6 of 10)

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide

N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 7 of 10)

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide
5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide
2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide
[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(2 or 3-hydroxy-pyrrolidin-1-yl)-methanone
5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide
5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide
[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl)-methanone
N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide
N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;
5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide
N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 8 of 10)

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 9 of 10)

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

FORMULA (I) COMPOUND TABLE
(continued, page 10 of 10)

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol

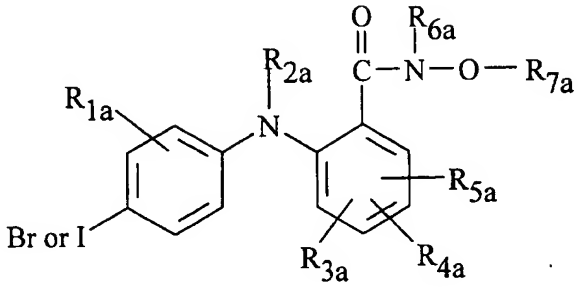
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol

[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

In another preferred embodiment, the MEK inhibitor is a compound of Formula II



II

In Formula (II), R_{1a} is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN. R_{2a} is hydrogen. Each of R_{3a}, R_{4a}, and R_{5a} is independently selected from hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, and $(O \text{ or } NH)_m$-$(CH_2)_n$-R_{9a}. R_{9a} is hydrogen, hydroxy, CO_2H or $NR_{10a}R_{11a}$; n is 0-4; and m is 0 or 1. Each of R_{10a} and R_{11a} is independently hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-(C_1-C_8 alkyl). R_{6a} is hydrogen, C_1-C_8 alkyl, (CO)-(C_1-C_8 alkyl), aryl, aralkyl, or C_3-C_{10} cycloalkyl. R_{7a} is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{10} (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a}). In Formula (II), any of the alkyl, alkenyl, aryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl, phenoxy, C_3-C_5 heteroaryl, or C_3-C_5 heteroaryloxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or $NR_{10a}R_{11a}$. The invention also encompasses pharmaceutically acceptable salts, esters, amides or prodrugs of each of the disclosed compounds.

Preferred embodiments of Formula (II) are those structures wherein:

(a) R_{1a} is H, methyl, fluoro, or chloro; (b) R_{2a} is H; R_{3a}, R_{4a}, and R_{5a} are each H, Cl, nitro, or F; (c) R_{6a} is H; (d) R_{7a} is methyl, ethyl, 2-propenyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopropylmethyl, or cyclopropylethyl; (e) the 4' position is I, rather than Br; (f) R_{4a} is F at the 4 position, para to the CO-N-R_{6a}-OR_{7a} group and meta to the bridging nitrogen; (f) R_{3a} or R_{5a} is F; (g) at least one of R_{3a}, R_{4a}, and R_{5a} is F; (h) R_{1a} is methyl or chloro; or (i) a combination of the above.

In a more preferred embodiment the MEK inhibitor is a compound selected from Formula (II) Compound Table below.

FORMULA (II) COMPOUND TABLE
(page 1 of 7)

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 2 of 7)

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-benzamide

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide

5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyloxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 3 of 7)

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide

5-Bromo-3-4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-ynyloxy)-benzamide

5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide

4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide

5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 4 of 7)

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-prop-2-ynyloxy)-benzamide

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-2-ynyloxy)-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 5 of 7)

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide

3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methyl-benzamide

2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide

2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 6 of 7)

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide

N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide

2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide

FORMULA (II) COMPOUND TABLE
(continued, page 7 of 7)

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide
N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide
2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide
2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide
2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide
2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide.

In the most preferred embodiment of this invention, a compound selected from the following is administered to a patient (ie, a mammal) in an amount that is effective to prevent or treat transplant rejection:

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD184352); 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD170611); 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD171984); 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD177168); 2-(2-Methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-5-bromobenzamide (PD 180841); 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 184161); 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD184386); 2-(2-Chloro-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluorobenzamide (PD 185625); 2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD 185848); 2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluorobenzamide (PD 188563); 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-

3,4,5-trifluorobenzamide (PD 198306); and 2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide (PD 203311); and the benzoic acid derivatives thereof. For example, the benzoic acid derivative of PD 198306 is 2-(2-Methyl-4-iodophenylamino)-3,4,5-trifluorobenzoic acid.

Additional preferred compounds include 2-(2-chloro-4-iodophenylamino)-5-chloro-N-cyclopropylmethoxy -3,4-difluorobenzamide (PD 297189), 2-(4-iodophenylamino)-N-cyclopropylmethoxy-5-chloro-3,4-difluorobenzamide (PD 297190), 2-(4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296771), 2-(2-chloro-4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296770), 5-chloro-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid (PD 296767); and 5-chloro-N-cyclopropylmethoxy -3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide (PD 298127).

Another preferred method according to this invention comprises administering to a mammal that has undergone a transplant, or is about to undergo a transplant, the immunosuppressive agent which is 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide.

Still another preferred method according to this invention employs the compound which is 2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide.

The invention further provides methods of synthesis and synthetic intermediates.

Other features and advantages of the invention are apparent from the detailed description, examples, and claims set forth.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the dose response ability of 2-(2-chloro-4-iodophenylamino)-N-cycloproplymethoxy-3,4-difluorobenzamide (PD 184352) to inhibit the cellular production of interleukin-2 (IL-2) in human peripheral blood mononuclear cells stimulated with concanavalin A (Con A).

Figure 2 shows the dose response ability of PD 184352 to inhibit the cellular production of IL-2 in human peripheral blood mononuclear cells stimulated with anti-CD3 plus anti-CD28.

Figure 3 shows the dose response ability of PD 184352 to inhibit cellular production of interferon-δ (IFN-δ) in cells stimulated with Con A.

Figure 4 shows the ability of PD 184352 to suppress the human mixed lymphocyte reaction (MLR) as measured by the uptake of tritiated thymidine (3H-TDR).

Figure 5 shows the dose response ability of PD 184352 to inhibit Con A induced T-cell proliferation.

Figure 6 shows the dose response ability of PD 184352 to inhibit T-cell proliferation induced by phytohemagglutinin (PHA)..

Figure 7 shows the lack of toxicity of PD 184352 in cells.

Figure 8 shows the inhibitory activity of several MEK inhibitors against MLR, IFN-gamma, and IL-2, and the ability of the compounds to inhibit PHA and Con A-induced proliferation with little or no toxicity (MTT). The compounds tested were PD 184352;

2-(2-methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD 171984);

2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 177168);

2-(2-chloro-4-iodophenylamino)-N-cycloproplymethoxy-3,4-difluoro-5-bromobenzamide (PD 184161); and

2-(2-chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD 184386).

Figure 9 shows the relative IL-2 suppressive activity of several phenyl amine compounds compared to rolipram and to dexamethasone (Dex).

Figure 10 shows the comparative activity of several phenyl amines, rolipram, and dexamethasone to suppress production of IFN-δ.

Figure 11 shows the human MLR suppressive activity of several phenyl amine MEK inhibitors compared to dexamethasone.

Figure 12 shows the ability of several phenyl amine MEK inhibitors to suppress human T-cell proliferation, compared to dexamethasone.

Figure 13 shows the percent cell death caused by several phenyl amine MEK inhibitors in the human MTT test.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a method for the prophylaxis of rejection of transplants in mammals, as well as control and maintenance of grafts. The invention is practiced by administering to a mammal that has undergone a transplant, or to a patient who is scheduled to undergo a transplant, an effective immunosuppressive amount of a selective MEK inhibitor to prevent or control the rejection of the transplanted organ, limb, cell(s), or tissue. For example, the method is practiced by administering a phenyl amine MEK inhibitor that is described in WO 98/37881. These are selective MEK inhibitors, namely they inhibit MEK 1 and MEK 2 without substantial inhibition of other enzymes. The method is ideally suited to prevent and control of rejection of kidney, liver, lung, and limb transplants.

The mammals to be treated according to this invention are patients who have undergone a transplant of an organ, a tissue, a limb, or cells, or who are about to undergo such transplant. Those skilled in the medical art are readily able to identify individual patients who are in need of an immunosuppressive agent in order to prevent or control the rejection of a foreign organ, limb, cell, or tissue.

The compounds of the present invention are MEK inhibitors. A MEK inhibitor is a compound that shows MEK inhibition when tested in the assays titled "Enzyme Assays" in United States Patent Number 5,525,625, column 6, beginning at line 35. The complete disclosure of United States Patent Number 5,525,625 is hereby incorporated by reference. An example of a MEK inhibitor is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran. Specifically, a compound is a MEK inhibitor if a compound shows activity in the assay titled "Cascade Assay for Inhibitors of the MAP Kinase Pathway," column 6, line 36 to column 7, line 4 of the United States Patent Number 5,525,625 and/or shows activity in the assay titled "In Vitro MEK Assay" at column 7, lines 4 to 27 of the above-referenced patent.

A. Terms

Some of the terms used herein are defined below in combination with their usage throughout this disclosure.

As used herein, the term "aryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from five to twelve carbon atoms. Examples of typical aryl groups include phenyl, naphthyl, and fluorenyl. The aryl may be substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Typical substituted aryl groups include 3-fluorophenyl, 3,5-dimethoxyphenyl, 4-nitronaphthyl, 2-methyl-4-chloro-7-aminofluorenyl, and the like.

The term "aryloxy" means an aryl group bonded through an oxygen atom, for example phenoxy, 3-bromophenoxy, naphthyloxy, and 4-methyl-1-fluorenyloxy.

"Heteroaryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from four to eleven carbon atoms and one, two, or three heteroatoms selected from O, S, or N. Examples include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, xanthenyl, pyronyl, indolyl, pyrimidyl, naphthyridyl, pyridyl, benzinnidazolyl, and triazinyl. The heteroaryl groups can be unsubstituted or substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Examples of substituted heteroaryl groups include chloropyranyl, methylthienyl, fluoropyridyl, amino-1,4-benzisoxazinyl, nitroisoquinolinyl, and hydroxyindolyl.

The heteroaryl groups can be bonded through oxygen to make heteroaryloxy groups, for example thienyloxy, isothiazolyloxy, benzofuranyloxy, pyridyloxy, and 4-methylisoquinolinyloxy.

The term "alkyl" means straight and branched chain aliphatic groups. Typical alkyl groups include methyl, ethyl, isopropyl, tert.-butyl, 2,3-dimethylhexyl, and 1,1-dimethylpentyl. The alkyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, as those terms are defined

herein. Typical substituted alkyl groups include chloromethyl, 3-hydroxypropyl, 2-dimethylaminobutyl, and 2-(hydroxymethylamino)ethyl. Examples of aryl and aryloxy substituted alkyl groups include phenylmethyl, 2-phenylethyl, 3-chlorophenylmethyl, 1,1-dimethyl-3-(2-nitrophenoxy)butyl, and 3,4,5-trifluoronaphthylmethyl. Examples of alkyl groups substituted by a heteroaryl or heteroaryloxy group include thienylmethyl, 2-furylethyl, 6-furyloxyoctyl, 4-methylquinolyloxymethyl, and 6-isothiazolylhexyl. Cycloalkyl substituted alkyl groups include cyclopropylmethyl, 2-cyclohexyethyl, piperidyl-2-methyl, 2-(piperidin-1-yl)-ethyl, 3-(morpholin-4-yl)propyl.

"Alkenyl" means a straight or branched carbon chain having one or more double bonds. Examples include but-2-enyl, 2-methyl-prop-2-enyl, 1,1-dimethyl-hex-4-enyl, 3-ethyl-4-methyl-pent-2-enyl, and 3-isopropyl-pent-4-enyl. The alkenyl groups can be substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, aryl, aryloxy, heteroaryl, or heteroyloxy, for example 2-bromoethenyl, 3-hydroxy-2-butenyl, 1-aminoethenyl, 3-phenylprop-2-enyl, 6-thienyl-hex-2-enyl, 2-furyloxy-but-2-enyl, and 4-naphthyloxy-hex-2-enyl.

"Alkynyl" means a straight or branched carbon chain having at least one triple bond. Typical alkynyl groups include prop-2-ynyl, 2-methyl-hex-5-ynyl, 3,4-dimethyl-hex-5-ynyl, and 2-ethyl-but-3-ynyl. The alkynyl groups can be substituted as the alkyl and alkenyl groups, for example, by aryl, aryloxy, heteroaryl, or heteroaryloxy, for example 4-(2-fluorophenyl)-but-3-ynyl, 3-methyl-5-thienylpent-4-ynyl, 3-phenoxy-hex-4-ynyl, and 2-furyloxy-3-methyl-hex-4-ynyl.

The alkenyl and alkynyl groups can have one or more double bonds or triple bonds, respectively, or a combination of double and triple bonds. For example, typical groups having both double and triple bonds include hex-2-en-4-ynyl, 3-methyl-5-phenylpent-2-en-4-ynyl, and 3-thienyloxy-hex-3-en-5-ynyl.

The term "cycloalkyl" means a nonaromatic ring or fused rings. Examples include cyclopropyl, cyclobutyl, cyclopenyl, cyclooctyl, bicycloheptyl, adamantyl, and cyclohexyl. The ring can optionally contain one, two, or three heteroatoms selected from O, S, or N. Such groups include tetrahydrofuryl, tetrahydropyrrolyl, octahydrobenzofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, octahydroindolyl, and octahydrobenzothiofuranyl. The cycloalkyl groups can be

substituted with the same substituents as an alkyl and alkenyl groups, for example, halo, hydroxy, aryl, and heteroaryloxy. Examples include 3-hydroxycyclohexyl, 2-aminocyclopropyl, 2-phenylpyrrolidinyl, and 3-thienylmorpholin-1-yl.

The term "maintenance" means controlling the tendency of a mammal to reject a cell, organ, limb, or tissue that has been transplanted into or onto the mammals body. The method is practiced by administering an amount of a selective MEK inhibitor that is effective to prevent or control the rejection.

The term "patient" means all animals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, horses, and pigs.

Selective MEK 1 or MEK 2 inhibitors are those compounds which inhibit the MEK 1 or MEK 2 enzymes, respectively, without substantially inhibiting other enzymes such as MKK3, PKC, Cdk2A, phosphorylase kinase, EGF, and PDGF receptor kinases, and C-src. In general, a selective MEK 1 or MEK 2 inhibitor has an IC_{50} for MEK 1 or MEK 2 that is at least one-fiftieth (1/50) that of its IC_{50} for one of the above-named other enzymes. Preferably, a selective inhibitor has an IC_{50} that is at least 1/100, more preferably 1/500, and even more preferably 1/1000, 1/5000, or less than that of its IC_{50} or one or more of the above-named enzymes.

B. Administration and Formulation

The MEK inhibitors of the present method can be administered to a patient as part of a pharmaceutically acceptable composition. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as

ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part

of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalamic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present method can be administered to a patient at dosage levels in the range of about 0.1 to about 1000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kg of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

The compounds of the present method can be administered as pharmaceutically acceptable salts, esters, amides, or prodrugs. The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is

incorporated herein by reference.)

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5 or 6 membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present method can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

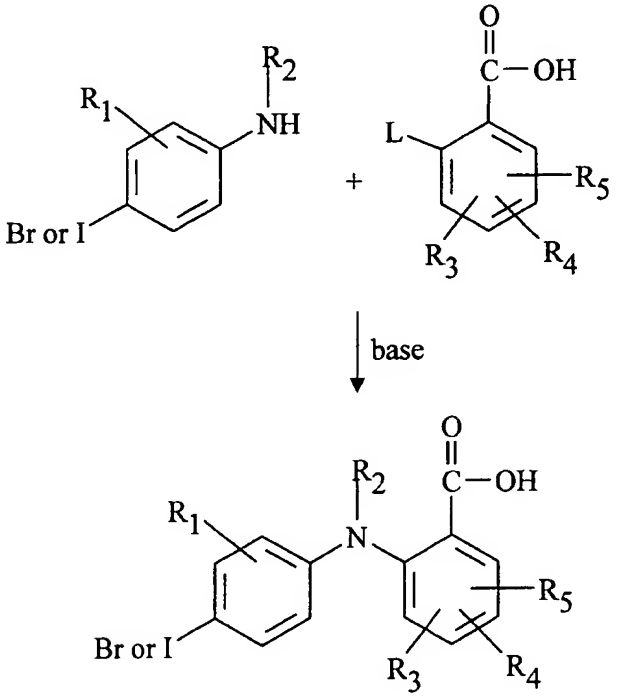
Some of the compounds of the present method can exist in different stereoisometric forms by virtue of the presence of chiral centers. It is contemplated that all stereoisometric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of this invention.

C. Synthesis

The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the specification, including the claims, in any way. After the priority date of the present disclosure, related syntheses and MEK inhibition data were also published in WO 99/01421 and WO 99/01426, hereby incorporated by reference.

The 2-(4-bromo and 4-iodo phenylamino)-benzoic acid derivatives of Formula (I) can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a benzoic acid having a leaving group at the 2-position to give a 2-(phenylamino)-benzoic acid. This process is depicted in Scheme 1.

Scheme 1



where L is a leaving group, for example halo such as fluoro.

The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of

the aniline in an unreactive organic solvent such as tetrahydrofuran or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium hydride, triethylamine, and Hunig's base. The reaction generally is carried out at a temperature of about -78°C to about 100°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

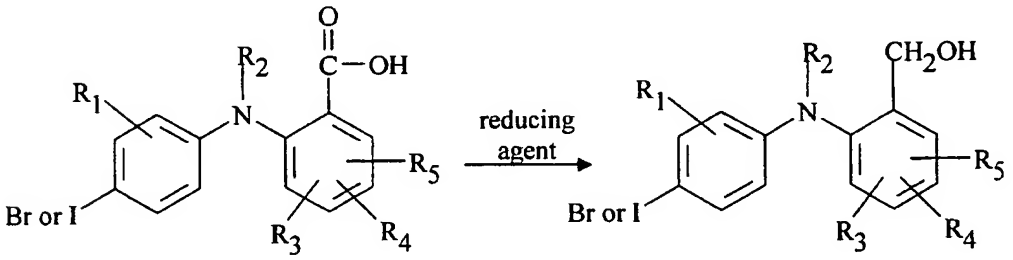
The 2-(phenylamino)-benzoic acid (e.g., Formula I, where R_7 is hydrogen) can be reacted with an organic or inorganic base such as pyridine, triethylamine, calcium carbonate, or sodium hydroxide to produce a pharmaceutically acceptable salt. The free acids can also be reacted with an alcohol of the formula HOR_7 (where R_7 is other than hydrogen, for example methyl) to produce the corresponding ester. Reaction of the benzoic acid with an alcohol can be carried out in the presence of a coupling agent. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)- phosphonium hexafluorophosphate (PyBrOP), and (benzotriazolyloxy) tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and alcohol derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

The benzamides of the invention, Formula (I)where Z is $CONR_6R_7$, are readily prepared by reacting the foregoing benzoic acids with an amine of the formula HNR_6R_7. The reaction is carried out by reacting approximately equimolar quantities of the benzoic acid and amine in an unreactive organic

solvent in the presence of a coupling reagent. Typical solvents are chloroform, dichloromethane, tetrahydrofuran, benzene, toluene, and xylene. Typical coupling reagents include DCC, EEDQ, PyBrOP, and PyBOP. The reaction is generally complete after about 10 minutes to about 2 hours when carried out at a temperature of about 0°C to about 60°C. The product amide is readily isolated by removing the reaction solvent, for instance by evaporation, and further purification can be accomplished by normal methods such as chromatography, crystallization, or distillation. The hydrazides (z = $CONHNR_{10}R_{11}$) are similarly prepared by coupling a benzoic acid with a hydrazine of the formula $H_2HNR_{10}R_{11}$.

The benzyl alcohols of the invention, compounds of Formula (I) where Z is CH_2OR_6 and R_6 is hydrogen, are readily prepared by reduction of the corresponding benzoic acid according to the following Scheme 2.

Scheme 2



Typical reducing agents commonly employed include borane in tetrahydrofuran. The reduction normally is carried out in an unreactive organic solvent such as tetrahydrofuran, and generally is complete within about 2 hours to about 24 hours when conducted at a temperature of about 0°C to about 40°C.

The following detailed examples illustrate specific compounds provided by this invention.

EXAMPLE 1

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid

To a stirring solution comprised of 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethenylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which temperature it was stirred for 2 days. The reaction mixture was concentrated. Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and then boiled over a steambath to low volume and cooled to room temperature. The off-white fibers were collected by vacuum filtration, rinsed with hexanes, and vacuum-oven dried. (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

^1H NMR (400 MHz; DMSO): δ 9.72 (s, 1H), 7.97 (dd, 1H, J = 7.0, 8.7 Hz), 7.70 (d, 1H, J = 1.5 Hz), 7.57 (dd, 1H, J = 8.4, 1.9 Hz), 7.17 (d, 1H, J = 8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

^{13}C NMR (100 MHz; DMSO): δ 169.87, 167.60, 165.12, 150.17, 150.05, 139.83, 138.49, 136.07, 135.31, 135.20, 135.07, 125.60, 109.32, 105.09, 104.87, 99.72, 99.46, 89.43, 17.52;

^{19}F NMR (376 MHz; DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C = O stretch) cm^{-1};

MS (CI) M+1 = 372.

Analysis calculated for $C_{14}H_{11}FINO_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

EXAMPLES 2-30

By following the general procedure of Example 1, the following benzoic acids and salts of Formula (I) were prepared.

Example No.	Compound	MP °C
2	3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	206-210
3	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	240.5-244.5
4	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	259.5-262
5	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	255-260
6	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	234-238
7	Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate	310-320 DEC
8	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	239.5-240
9	2-(2-Chloro-4-iodo-phenylamino)-5-nitro-benzoic acid	289-293
10	4-Fluoro-2-(3-fluoro-4-iodo-2-methyl-phenylamino)-benzoic acid	233-235
11	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid	264-267
12	2-(2-Fluoro-4-iodo-phenylamino)-5-nitro-benzoic acid	256-258
13	2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid	218.5-220
14	2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid	285-288 DEC
15	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid	230-234
16	3-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-221
17	3,4-Difluoro-2-(4-iodo-2-methoxy-phenylamino)-benzoic acid	230-233
18	4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	245-255 DEC

Example No.	Compound	MP °C
19	2-(4-Iodo-2-methyl-phenylamino)-benzoic acid	218-223
20	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	243-46
21	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	241-245
22	2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-222
23	4-Fluoro-2-(3-chloro-4-iodo-2-methyl-phenylamino)-benzoic acid	248-252.5
24	2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid	208-211
25	3-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	232-233
26	2-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	179-182
27	4-Fluoro2-(2,3-dimethyl-4-iodo-2-methyl-phenylamino)benzoic acid	258-261
28	5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	209.5-211
29	2-Chloro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	171-175
30	2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid	251-263

EXAMPLE 31

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirring solution comprised of 0.1020 g (0.2632 mmol) of 5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid, 0.1 mL (1.7 mmol) of ethanolamine, and 0.05 mL (0.29 mmol) of diisopropylethylamine in 5 mL of a 1:1 (v/v) tetrahydrofuran-dichloromethane solution was added 0.15 g (0.29 mmol) of solid PyBOP powder directly. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The crude residue was partitioned between ether (50 mL) and 10% aqueous hydrochloric acid (50 mL). The organic phase was washed with 10% aqueous sodium hydroxide (50 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a yellow-brown oil which was crystallized from hexanes-ether to afford 0.0831 g (73%) of a green-yellow powder; mp 120-121°C;

^{1}H NMR (400 MHz; $CDCl_3$): δ 9.11 (s, 1H), 7.56 (d, 1H, J = 1.4 Hz), 7.46-7.41 (m, 2H), 7.20 (dd, 1H, J = 8.9, 2.4 Hz), 7.00 (t, 2H, J = 9.6 Hz), 6.55 (broad t, 1H), 3.86 (t, 2H, J = 5.0 Hz), 3.61 (dd, 2H, J = 10.1, 5.5 Hz), 2.23 (s, 3H), 1.56 (broad s, 1H);

IR (KBr) 3297 (O-H stretch), 1627 (C = O stretch) cm^{-1};

MS (CI) M+1 = 431.

Analysis calculated for $C_{16}H_{16}ClIN_2O_2$:

C, 44.62; H, 3.74; N, 6.50.

Found: 44.63; H, 3.67; N, 6.30.

EXAMPLES 32-48

By following the general procedure of Example 31, the following benzamides were prepared by reacting the corresponding benzoic acid with the corresponding amine.

Example No.	Compound	MP °C
32	4-Methoxy-N-(4-methoxy-phenyl)-3-nitro-benzamide	153.5-156
33	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	158
34	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide	102.5-104.5
35	N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	90-91
36	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	oil
37	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide	285-288 DEC
38	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	180-182
39	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	137-138

Example No.	Compound	MP °C
40	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	170-173
41	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide	69-71
42	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	132-133.4
43	N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	oil
44	4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide	122-124
45	N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	91-93
46	N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	97-99
47	5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	118-120
48	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	142.5-144

EXAMPLE 49

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.50 g, 1.35 mmol) was dissolved in 6 mL (6 mmol) of cold 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran solution. The reaction mixture was stirred under nitrogen atmosphere at room temperature overnight. The reaction was quenched with 80 mL of methanol. Concentration in vacuo produced a clear tan oil which was purified by MPLC. Elution with dichloromethane afforded 0.4285 g (89%) of a white solid; mp 99-100.5°C;

^{1}H NMR (400 MHz; DMSO): δ 7.57 (d, 1H, J=1.7 Hz), 7.45 (dd, 1H, J=8.4, 1.9 Hz), 7.39 (s, 1H), 7.29 (t, 1H, J=7.5 Hz), 6.89 (d, 1H, J=8.4 Hz), 6.67-6.60 (m, 1H), 5.47 (t, 1H, J=5.5 Hz), 4.49 (d, 2H, 5.1 Hz), 2.14 (s, 3H);

IR (KBr) 3372 (O-H stretch) cm^{-1};

MS (CI) M+1 = 358.

Analysis calculated for $C_{14}H_{13}FINO$:

C, 47.08; H, 3.67; N, 3.92.

Found: C, 47.17; H, 3.75; N, 3.72.

EXAMPLE 50-52

The following benzyl alcohols were prepared by the general procedure of Example 49.

Example No.	Compound	MP °C
50	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	82-85
51	[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol	126.5-128.5
52	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	60.5-63.5

Several invention compounds of Formula (I) were prepared utilizing combinatorial synthetic techniques. The general procedure is as follows:

To a 0.8-mL autosampler vial in a metal block was added 40 µL of a 0.5 M solution of the acid in DMF and 40 µL of the reagent amine (2 M solution in Hunig's base and 1 M in amine in DMF). A 0.5 M solution of PyBrop was freshly prepared and 50 µL were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm × 25 cm, 5 µM spherical silica, pore size 115 A derivatized with C-18, the sample was eluted at 4.7 mL/min with

a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes). Fractions were collected by monitoring at 214 nM. The residue was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield.

EXAMPLES 53-206

The following compounds of Formula I were prepared by combinatorial methodology:

Example No.	Compound	MS M-H
53	5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	510
54	N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	462
55	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	577
56	3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	432
57	N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	444
58	3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	446
59	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	564
60	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	571
61	4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	414
62	5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	551

Example No.	Compound	MS M-H
63	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	580
64	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	501
65	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	485
66	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	493
67	N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
68	N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	460
69	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide	384
70	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	483
71	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	495
72	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	513
73	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide	480
74	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	467
75	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide	453
76	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	557
77	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	479
78	2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide	425

Example No.	Compound	MS M-H
79	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	461
80	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	475
81	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide	445
82	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide	400
83	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	437
84	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide	474
85	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide	450
86	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide	431
87	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide	444
88	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide	451
89	5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	557*
90	5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	541*
91	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide	487
92	5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	601*
93	5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	486*

Example No.	Compound	MS M-H
94	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	497*
95	(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanone	466
96	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	484*
97	5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	530*
98	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide	518*
99	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide	562*
100	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone	499
101	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid phenethyl ester	501
102	N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide	568*
103	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone	455
104	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	460
105	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	528*
106	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	542*
107	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	468*
108	5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	472*
109	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide	502*

Example No.	Compound	MS M-H
110	5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	445*
111	5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	516*
112	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	482*
113	5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	489*
114	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	556*
115	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide	529*
116	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	500*
117	5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	500*
118	5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	514*
119	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	512*
120	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide	509*
121	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide	544*
122	N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	470*
123	5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	516*
124	N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	456*
125	5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429*

Example No.	Compound	MS M-H
126	N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	484*
127	N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	511*
128	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	544*
129	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide	523*
130	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone	439
131	5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	558*
132	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	484*
133	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	496*
134	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-	482
135	N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide	500*
136	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	443
137	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	495*
138	N-(3-Dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	483*
139	N-(2-Diisopropylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide	498*
140	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	490
141	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	506

Example No.	Compound	MS M-H
142	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	536
143	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-thiobenzoic acid S-benzyl ester	503
144	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	476
145	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	492
146	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409
147	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429
148	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	413
149	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	475
150	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	593*
151	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	567
152	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
153	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	521

Example No.	Compound	MS M-H
154	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	440
155	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	486
156	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
157	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	459
158	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409
159	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	583
160	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	538
161	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
162	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436
163	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	469
164	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	475
165	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	646
166	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	598
167	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436

Example No.	Compound	MS M-H
168	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	565
169	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	469
170	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	473
171	N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
172	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	519
173	N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	502
174	N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	559
175	N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
176	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	581
177	2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide	500
178	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	567
179	N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	451
180	5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	467
181	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	533
182	5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	511
183	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	489
184	N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	478

Example No.	Compound	MS M-H
185	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	538
186	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	477
187	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	431
188	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	475
189	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	488
190	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	477
191	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	523
192	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
193	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	427
194	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	461
195	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	442
196	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	415
197	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
198	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411
199	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	540
200	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438
201	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411

Example No.	Compound	MS M-H
202	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	585
203	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
204	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	601
205	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	522
206	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438

* M+H

EXAMPLE 207

Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

Step a: Preparation of 5-chloro-2-fluoro-benzaldehyde

To a solution of 1-chloro-4-fluorobenzne (13.06 g, 0.1 mol) in THF (180 mL), at -78°C, LDA (2M solution in THF, 50 mL, 0.1 mol) was added drop wise. After stirring at -78°C for 1.5 hours, DMF (8 mL) was added to the reaction mixture and allowed to warm up to room temperature overnight. The reaction mixture was partitioned between water and Et_2O. The Et_2O layer was dried ($MgSO_4$) and the solvent removed in vacuum to give 14.95 g (94%) yield of crude aldehyde: ^1H NMR ($CDCl_3$): δ, 10.3 (s, -C(=O)H).

Step b: Preparation of 5-chloro-2-fluoro-benzaldehyde oxime

A solution of 5-chloro-2-fluoro-benzaldehyde (10 g, 0.0631 mol), hydroxylamine hydrochloride (6.57 g, 0.0946 mol) and pyridine (8.3 mL, 0.1010 mol) in EtOH (100 mL) was heated at 75°C (oil bath temperature) for 1 hour and the solvent removed under vacuum to give an oil. The oil was partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and the solvent removed under vacuum to give crude aldoxime as a solid. The

solid was purified by medium pressure liquid chromatography on silica. Elution with CH_2Cl_2 gave 4.87 g (28%) of the aldoxime as white solid: mp 95-97°C;

Analysis calculated for C_7H_5NOFCl:

C, 48.44; H, 2.90; N, 8.07.

Found: C, 48.55; H, 2.69, N, 7.90.

Step c: Preparation of 5-chloro-2-fluoro-benzonirile

A solution of the 5-chloro-2-fluoro-benzaldehyde oxime (3.15 g, 0.0182 mol) in acetic anhydride (150 mL) was refluxed for 16 hours. The reaction mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (200 mL) solution. The mixture was extracted with Et_2O. The Et_2O layer was dried (K_2CO_3) and the solvent removed to give the product as an oily solid. The product was used without further purification in the next step.

Step d: Preparation of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole

A mixture of 5-chloro-2-fluoro-benzonitrile (2.84 g, 0.01823 mol), butanol (15 mL), sodium azide (1.543 g, 0.0237 mol), acetic acid (1.36 mL, 0.0237 mol) was refluxed for 24 hours. The reaction mixture was cooled to room temperature, additional 1.543 g sodium azide added, and the reaction mixture refluxed for additional 24 hours. After cooling to room temperature, Et_2O (100 mL) and 10% aqueous NaOH (200 mL) were added sequentially. The mixture was vigorously stirred. The aqueous layer was separated, cooled with ice-methanol bath (-15°C) and acidified to pH 1 with conc. HCl. A gray solid precipitated. The solid was dried in vacuum at 50°C to give 1.76 g (49%) of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole: mp partial melt at 110°C, complete melting at 124°C);

^1H (400 Mz, $CDCl_3$): δ 8.19-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.61-7.52 (m, 1H);

^{13}C (100 Mz, $CDCl_3$): δ 159.00, 156.49, 140.88, 133.02, 132.93, 130.73, 129.23, 129.21, 129.08, 126.05, 118.96, 118.73, 114.50;

MS (CI) M+1 = 199 (100), M = 198 (6).

Step e: Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

To a solution of 2-methyl-4-iodoaniline (3.52 g, 0.0151 mol) in THF (25 mL) at -78°C, LDA (2 molar solution in THF, 11.33 mL, 0.02267 mol) was added dropwise. After stirring for 0.5 hours, a solution of 1-(tetrazol-5-yl)-2-fluoro-5-chlorobenzene (1.5 g, 0.00756 mol) in THF (15 mL) was added dropwise. The reaction was stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous conc. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent removed giving a crude product as an oil. The oil with CH_2Cl_2->CH_2Cl_2:MeOH (9.7:0.3) gave 1.5 g (48%) of the desired product:

mp 205-208°C; ^1H (400 Mz, DMSO): δ 9.13 (s, 1H), 8.00-7.99 (s, 1H), 7.69 (s, 1H), 7.55-7.52 (m, 1H), 7.43-7.40 (m, 1H), 7.12-7.05 (m, 1H), 2.24 (s, 3H); ^{13}C (100 Mz, $CDCl_3$): δ 141.87, 139.28, 138.88, 135.47, 133.71, 131.65, 128.15, 123.69, 121.94, 116.68, 87.79, 17.22; MS (CI) M+2 = 413 (44), M+1 = 412 (85), M = 411 (100).

Analysis calculated for $C_{14}H_{11}N_5ClI \cdot 0.5H_2O$:

C, 39.97; H, 2.87; N, 16.65.

Found: C, 38.87, H, 2.77; N, 16.47.

The following tetrazole substituted phenylamines were prepared by following the general procedure of Example 207.

EXAMPLE 208

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine, mp 231°C (dec)

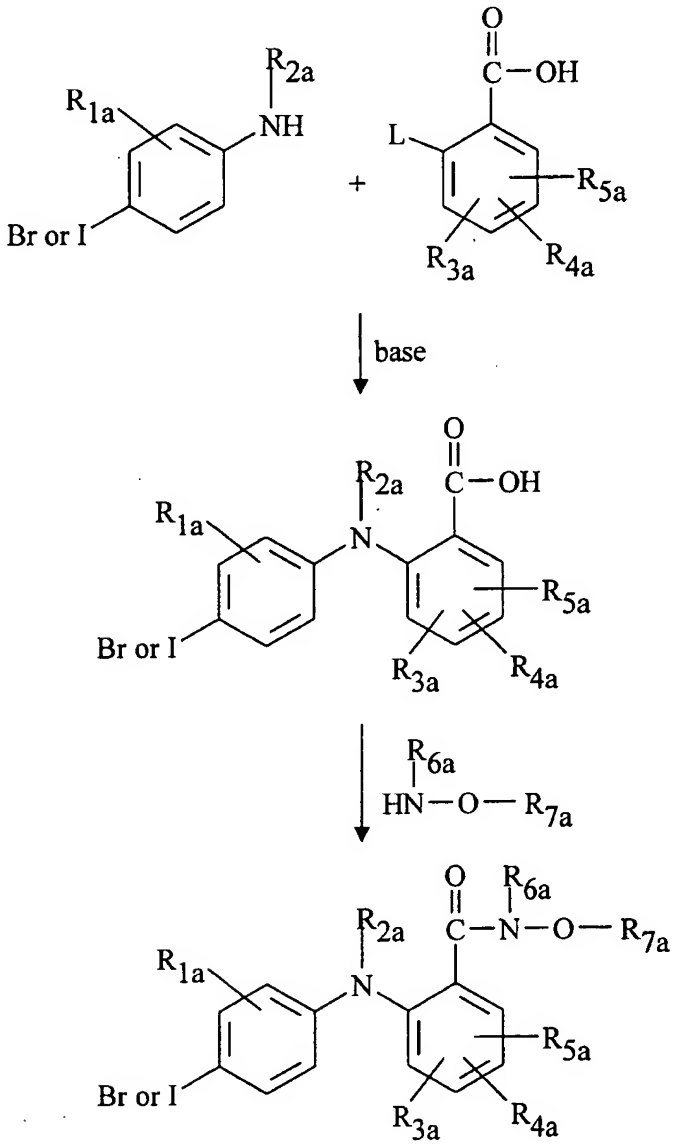
EXAMPLE 209

[4-nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine, mp 205-208°C.

The 4-bromo and 4-iodo phenylamino benzhydroxamic acid derivatives of Formula II can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic

chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a benzoic acid having a leaving group at the 2-position to give a phenylamino benzoic acid, and then reacting the benzoic acid phenylamino derivative with a hydroxylamine derivative (Scheme 3).

Scheme 3



where L is a leaving group, for example halo such as fluoro, chloro, bromo or iodo, or an activated hydroxy group such as a diethylphosphate, trimethylsilyloxy, p-nitrophenoxy, or phenylsulfonoxy.

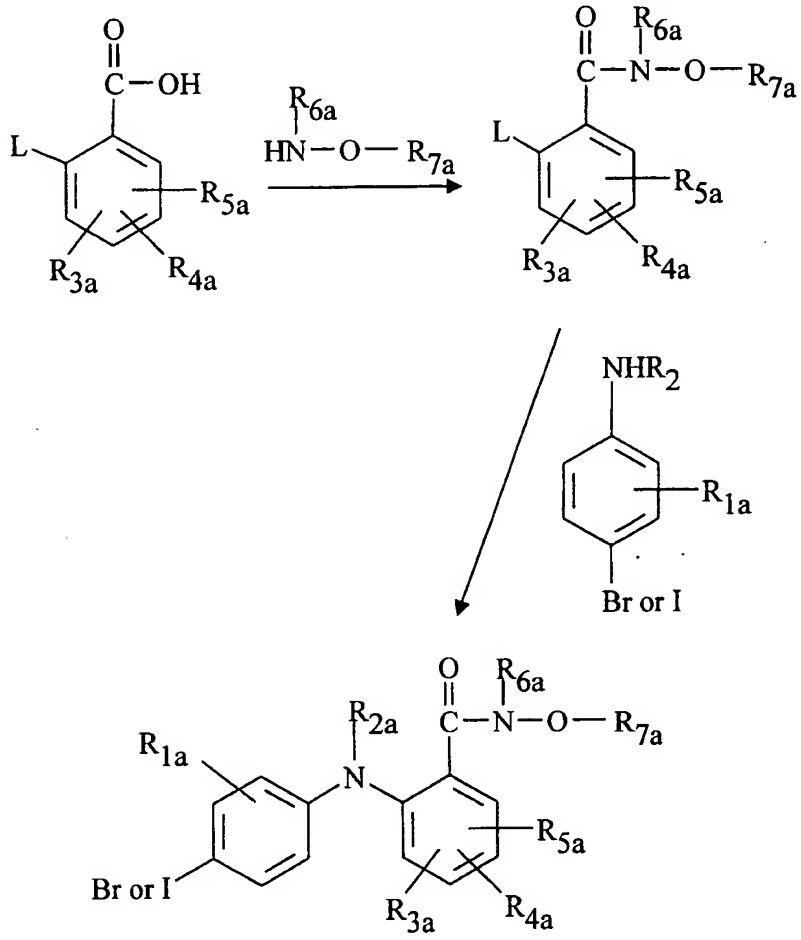
The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of the aniline in an unreactive organic solvent such as tetrahydrofuran, or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium hydride, and sodium amide. The reaction generally is carried out at a temperature of about -78°C to about 25°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

The phenylamino benzoic acid next is reacted with a hydroxylamine derivative $HNR_{6a}OR_{7a}$ in the presence of a peptide coupling reagent. Hydroxylamine derivatives that can be employed include methoxylamine, N-ethyl-isopropoxy amine, and tetrahydro-oxazine. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBrOP) and (benzotriazolyloxy)tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and hydroxylamino derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

An alternative method for making the invention compounds involves first converting a benzoic acid to a hydroxamic acid derivative, and then reacting the

hydroxamic acid derivative with an aniline. This synthetic sequence is depicted in Scheme 4.

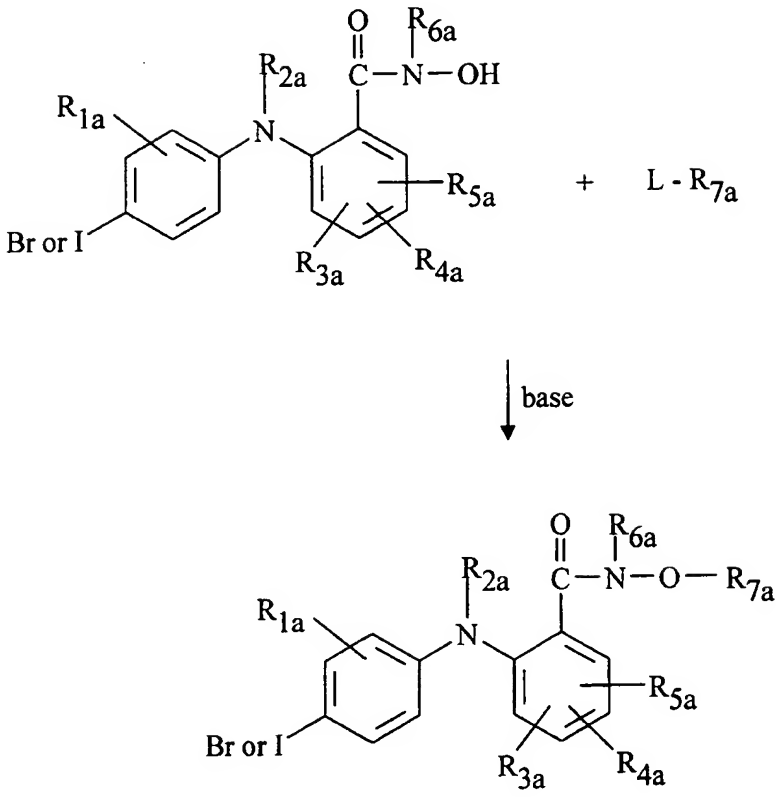
Scheme 4



where L is a leaving group. The general reaction conditions for both of the steps in Scheme 4 are the same as those described above for Scheme 3.

Yet another method for making invention compounds comprises reacting a phenylamino benzhydroxamic acid with an ester forming group as depicted in Scheme 5.

Scheme 5



where L is a leaving group such as halo, and a base is triethylamine or diisopropylamine.

The synthesis of compounds of Formula (II) is further illustrated by the following detailed examples.

EXAMPLE 1a

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

(a) Preparation of 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

To a stirred solution containing 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which

temperature the mixture was stirred for 2 days. The reaction mixture was concentrated by evaporation of the solvent under reduced pressure. Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and then concentrated over a steambath to low volume (10 mL) and cooled to room temperature. The off-white fibers which formed were collected by vacuum filtration, rinsed with hexane, and dried in a vacuum-oven (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

^1H NMR (400 MHz, DMSO): δ 9.72 (s, 1H), 7.97 (dd, 1H, J=7.0, 8.7 Hz), 7.70 (d, 1H, J=1.5 Hz), 7.57 (dd, 1H, J=8.4, 1.9 Hz), 7.17 (d, 1H, J=8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 169.87, 166.36 (d, J_{C-F}=249.4 Hz), 150.11 (d, J_{C-F}=11.4 Hz), 139.83, 138.49, 136.07, 135.26 (d, J_{C-F}=11.5 Hz), 135.07, 125.60, 109.32, 104.98 (d, J_{C-F}=21.1 Hz), 99.54 (d, J_{C-F}=26.0 Hz), 89.43, 17.52;

^{19}F NMR (376 MHz, DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C=O stretch)cm^{-1};

MS (CI) M+1 = 372.

Analysis calculated for $C_{14}H_{11}FINO_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

(b) Preparation of 4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirred solution of 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.6495 g, 0.001750 mol), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.2590 g, 0.002211 mol), and diisopropylethylamine (0.40 mL, 0.0023 mol) in 31 mL of an equivolume tetrahydrofuran-dichloromethane solution was added 1.18 g (0.00227 mol) of solid PyBOP ([benzotriazolyloxy]tripyrrolidino phosphonium hexafluorophosphate, Advanced ChemTech) directly. The reaction mixture was stirred for 30 minutes after which time it was concentrated in vacuo. The brown oil was treated with 10% aqueous hydrochloric acid. The suspension

was extracted with ether. The organic extraction was washed with 10% sodium hydroxide followed by another 10% hydrochloric acid wash, was dried ($MgSO_4$) and concentrated in vacuo to afford 1.0 g of a light-brown foam. This intermediate was dissolved in 25 mL of ethanolic hydrogen chloride, and the solution was allowed to stand at room temperature for 15 minutes. The reaction mixture was concentrated in vacuo to a brown oil that was purified by flash silica chromatography. Elution with a gradient (100 % dichloromethane to 0.6 % methanol in dichloromethane) afforded 0.2284 g of a light-brown viscous oil. Scratching with pentane-hexanes and drying under high vacuum afforded 0.1541 g (23%) of an off-white foam; mp 61-75°C;

^1H NMR (400 MHz, DMSO): δ 11.34 (s, 1H), 9.68 (s, 1H), 9.18 (s, 1H), 7.65 (d, 1H, J=1.5 Hz), 7.58 (dd, 1H, J=8.7, 6.8 Hz), 7.52 (dd, 1H, J=8.4, 1.9 Hz), 7.15 (d, 1H, J=8.4 Hz), 6.74 (dd, 1H, J=11.8, 2.4 Hz), 6.62 (ddd, 1H, J=8.4, 8.4, 2.7 Hz), 2.18 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 165.91, 164.36 (d, J_{C-F}=247.1 Hz), 146.78, 139.18, 138.77, 135.43, 132.64, 130.60 (d, J_{C-F}=11.5 Hz), 122.23, 112.52, 104.72 (d, J=22.1 Hz), 100.45 (d, J_{C-F}=25.2 Hz), 86.77, 17.03;

^{19}F NMR (376 MHz, DMSO): δ -107.20 to -107.27 (m);

IR (KBr) 3307 (broad, O-H stretch), 1636 (C=O stretch) cm^{-1};

MS (CI) M+1 = 387.

Analysis calculated for $C_{14}H_{12}FIN_2O_2$:

C, 43.54; H, 3.13; N, 7.25.

Found: C, 43.62; H, 3.24; N, 6.98.

EXAMPLE 2a

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

(a) Preparation of 5-Bromo-2,3,4-trifluorobenzoic acid

To a stirred solution comprised of 1-bromo-2,3,4-trifluorobenzene (Aldrich, 99%; 5.30 g, 0.0249 mol) in 95 mL of anhydrous tetrahydrofuran cooled to -78°C was slowly added 12.5 mL of 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene solution (Aldrich). The mixture was stirred

for 1 hour and transferred by canula into 700 mL of a stirred saturated ethereal carbon dioxide solution cooled to -78°C. The cold bath was removed, and the reaction mixture was stirred for 18 hours at ambient temperature. Dilute (10%) aqueous hydrochloric acid (ca. 500 mL) was poured into the reaction mixture, and the mixture was subsequently concentrated on a rotary evaporator to a crude solid. The solid product was partitioned between diethyl ether (150 mL) and aq. HCl (330 mL, pH 0). The aqueous phase was extracted with a second portion (100 mL) of diethyl ether, and the combined ethereal extracts were washed with 5% aqueous sodium hydroxide (200 mL) and water (100 mL, pH 12). These combined alkaline aqueous extractions were acidified to pH 0 with concentrated aqueous hydrochloric acid. The resulting suspension was extracted with ether (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and subjected to high vacuum until constant mass was achieved to afford 5.60 g (88% yield) of an off-white powder; mp 139-142.5°C;

^1H NMR (400 MHz, DMSO): δ 13.97 (broad s, 1H, 8.00-7.96 (m, 1H);

^{13}C NMR (100 MHz, DMSO): δ 162.96, 129.34, 118.47, 104.54 (d, J_{C-F}=22.9 Hz);

^{19}F NMR (376 MHz, DMSO): δ -120.20 to -120.31 (m), -131.75 to -131.86 (m), -154.95 to -155.07 (m);

IR (KBr) 1696 (C=O stretch)cm^{-1};

MS (CI) M+1 = 255.

Analysis calculated for $C_{74}H_{21}BrF_3O_2$:

C, 32.97; H, 0.79; N, 0.00; Br, 31.34; F, 22.35.

Found: C, 33.18; H, 0.64; N, 0.01; Br, 30.14; F, 22.75.

(b) Preparation of 5-Bromo-3.4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

To a stirred solution comprised of 1.88 g (0.00791 mol) of 2-amino-5-iodotoluene in 10 mL of tetrahydrofuran at -78°C was added 6 mL (0.012 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for

10 minutes, after which time a solution of 1.00 g (0.00392 mol) of 5-bromo-2,3,4-trifluorobenzoic acid in 15 mL of tetrahydrofuran was added. The cold bath was subsequently removed, and the reaction mixture stirred for 18 hours. The mixture was concentrated, and the concentrate was treated with 100 mL of dilute (10%) aqueous hydrochloric acid. The resulting suspension was extracted with ether (2 × 150 mL), and the combined organic extractions were dried ($MgSO_4$) and concentrated in vacuo to give an orange solid. The solid was triturated with boiling dichloromethane, cooled to ambient temperature, and collected by filtration. The solid was rinsed with dichloromethane, and dried in the vacuum-oven (80°C) to afford 1.39 g (76%) of a yellow-green powder; mp 259.5-262°C;

^1H NMR (400 MHz, DMSO): δ 9.03 (s, 1H), 7.99 (dd, 1H, J=7.5, 1.9 Hz), 7.57 (dd, 1H, J=1.5 Hz), 7.42 (dd, 1H, J=8.4, 1.9 Hz), 6.70 (dd, 1H, J=8.4, 6.0 Hz), 2.24 (s, 3H);

^{19}F NMR (376 MHz, DMSO): δ -123.40 to -123.47 (m); -139.00 to -139.14 (m);

IR (KBr) 1667 (C=O stretch)cm^{-1};

MS (CI) M+1 = 469.

Analysis calculated for $C_{14}H_9BrF_2INO_2$:

C, 35.93; H, 1.94; N, 2.99; Br, 17.07; F, 8.12; I, 27.11.

Found: C, 36.15; H, 1.91; N, 2.70; Br, 16.40; F, 8.46; I, 26.05.

(c) Preparation of 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirred solution comprised of 5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.51 g, 0.0011 mol), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.15 g, 0.0013 mol), and diisopropylethylamine (0.25 mL, 0.0014 mol) in 20 mL of an equivolume tetrahydrofuran-dichloromethane solution was added 0.6794 g (0.001306 mol) of solid PyBOP (Advanced ChemTech) directly. The reaction mixture was stirred at 24°C for 10 minutes, and then was concentrated to dryness in vacuo. The concentrate was suspended in 100 mL of 10% aqueous hydrochloric acid. The suspension was extracted with 125 mL of diethyl ether. The ether layer was separated, washed with 75 mL of 10% aqueous sodium hydroxide, and then with 100 mL of dilute

acid. The ether solution was dried ($MgSO_4$) and concentrated in vacuo to afford 0.62 g (100%) of an off-white foam. The foam was dissolved in ca. 15 mL of methanolic hydrogen chloride. After 5 minutes, the solution was concentrated in vacuo to an oil, and the oil was purified by flash silica chromatography. Elution with dichloromethane: dichloromethane-methanol (99:1) afforded 0.2233 g (42%) of a yellow powder. The powder was dissolved in diethyl ether and washed with dilute hydrochloric acid. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 0.200 g of a foam. This product was triturated with pentane to afford 0.1525 g of a powder that was repurified by flash silica chromatography. Elution with dichloromethane afforded 0.0783 g (15%) of an analytically pure title compound, mp 80-90°C;

^1H NMR (400 MHz, DMSO): δ 11.53 (s, 1H), 9.38 (s, 1H), 8.82 (s, 1H), 7.70 (dd, 1H, J=7.0, 1.9 Hz), 7.53 (s, 1H), 7.37 (dd, 1H, J=8.4, 1.9 Hz), 6.55 (dd, 1H, J=8.2, 6.5 Hz), 2.22 (s, 3H);

^{19}F NMR (376 MHz, DMSO): δ -126.24 to -126.29 (m), -137.71 to -137.77 (m);

IR (KBr) 3346 (broad, O-H stretch), 1651 (C=O stretch)cm^{-1};

MS (CI) M+1 = 484.

Analysis calculated for $C_{14}H_{10}BrF_2IN_2O_2$:

C, 34.81; H, 2.09; N, 5.80.

Found: C, 34.53; H, 1.73; N, 5.52.

Examples 3a to 12a in the table below were prepared by the general procedure of Examples 1a and 2a.

EXAMPLES 13a-77a

Examples 13a to 77a were prepared utilizing combinatorial synthetic methodology by reacting appropriately substituted phenylamino benzoic acids

(e.g., as shown in Scheme 1) and hydroxylamines (e.g., (NHR_{6a})-O-R_{7a}). A general method is given below:

To a 0.8-mL autosampler vial in a metal block was added 40 μL of a 0.5 M solution of the acid in DMF and 40 μL of the hydroxylamine (2 M solution

in Hunig's base and 1 M in amine in DMF). A 0.5 M solution of PyBrOP was freshly prepared, and 50 μL were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm × 25 cm, 5 μM spherical silica, pore Size 115 A derivatized with C-18, the sample was eluted at 4.7 mL/min with a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes.) Fractions were collected by monitoring at 214 nM. The desired fractions were evaporated using a Zymark Turbovap. The product was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield. The structure was confirmed by mass spectroscopy.

EXAMPLES 3a-77a

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
3a	2-(4-bromo-2-methyl-phenylamino)-4-fluoro-N-hydroxy-benzamide	56-75 dec	523
4a	5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide	65 dec	
5a	5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide	62-67	
6a	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(terahydropyran-2-yloxy)benzamide	105-108	
7a	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxybenzamide	64-68	
8a	4-Fluoro-N-hydroxy-2-(4-fluoro-2-methyl-phenylamino)-benzamide	119-135	
9a	4-Fluoro-N-hydroxy-2-(2-methyl phenylamino)-benzamide	101-103	
10a	4-Fluoro-2-(4-fluor-2-methyl-phenylamino)-N-(terahydropyran-2-yloxy)benzamide	142-146	
11a	4-Fluoro-N-hydroxy-2-(4-cluoro-2-methyl-phenylamino)-benzamide	133.5-135	

Example No.	Compound	Melting Point (°C)	MS (M-H$^+$)
12a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide	107-109.5	
13a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide		399
14a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide		417
15a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-methoxy-benzamide		369
16a	2-(4-Bromo-2-methyl-phenylamino)-N-ethoxy-3,4-difluoro-benzamide		342* (M-EtO)
17a	5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		509
18a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		445
19a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-isopropoxy-benzamide		397
20a	4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		465

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
21a	3,4-Difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		483
22a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(furan-3-ylmethoxy)-benzamide		435
23a	5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		561
24a	5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		536
25a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		423
26a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		441
27a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide		455
28a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(1-methyl-prop-2-ynyloxy)-benzamide		407
29a	N-(But-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		455

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
30a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-3,4-difluoro-benzamide		407
31a	5-Bromo-N-(but-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		533
32a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenyl-prop-2-ynyloxy)-benzamide		517
33a	3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenyl-prop-2-ynyloxy)-benzamide		469
34a	3,4-Difluoro-N-[3-(3-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		535
35a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-[3-(3-fluoro-phenyl)-prop-2-ynyloxy]-benzamide		487
36a	3,4-Difluoro-N-[3-(2-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		535
37a	5-Bromo-3,4-difluoro-N-[3-(2-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		613

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
38a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenyl-pent-2-en-4-ynyloxy)-benzamide		557* *(M+H)
39a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-methyl-5-phenyl-pent-2-en-4-ynyloxy)-benzamide		510
40a	N-Ethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		431
41a	2-(4-Bromo-2-methyl-phenylamino)-N-ethoxy-3,4-difluoro-benzamide		383
42a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		427
43a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		445
44a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-propoxy-benzamide		397
45a	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		523
46a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		427

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
47a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		445
48a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-isopropoxy-benzamide		397
49a	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		523
50a	N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457
51a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclobutyloxy-3,4-difluoro-benzamide		409
52a	N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		453
53a	N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		471
54a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclopentyloxy-3,4-difluoro-benzamide		423
55a	N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		439
56a	N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
57a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide		409
58a	5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)		435
59a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxy-ethoxy)-benzamide		505
60a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxy-ethoxy)-benzamide		523
61a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-phenoxy-ethoxy)-benzamide		475
62a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiophen-2-ylmethoxy)-benzamide		481
63a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiophen-2-ylmethoxy)-benzamide		499
64a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)-benzamide		451
65a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-allyloxy)-benzamide		439

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
66a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-allyloxy)-benzamide		457
67a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-methyl-allyloxy)-benzamide		410
68a	N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		439
69a	N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457
70a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-3,4-difluoro-benzamide		410
71a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		441
72a	N-(But-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		455
73a	2-(4-Bromo-2-methyl-phenylamino)-N-(4,4-dimethyl-pent-2-ynyloxy)-3,4-difluoro-benzamide		449
74a	N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
75a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-3,4-difluoro-benzamide		410
76a	N-(3-tert-butyl-propyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		479
77a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide		577

PHYSICAL DATA FOR SELECTED COMPOUNDS

PD 0171984

mp 80-90 °C

PD 0184161

mp 174-175 °C

PD 0203311

mp 141-144 °C

PD 0297189

mp 167-169 °C

^{1}H-NMR (400 MHz; DMSO) δ 11.70 (s, 1H), 8.59 (s, 1H), 7.55 (s, 1H), 7.43 (d, 1H, J=6.5 Hz), 7.27 (d,1H, J=8.7 Hz), 6.46 (m, 1H), 3.42 (d, 2H, J=7.0 Hz), 0.84 (m, 1H), 0.27 (m, 2H), 0.00 (m, 2H)

PD 0297190

mp 125.5-133 °C

^{1}H-NMR (400 MHz; DMSO) δ 11.48 (s, 1H), 8.32 (s, 1H), 7.34 (d, 1H, J=7.5 Hz), 7.28 (d, 2H, J=8.2 Hz), 6.48 (d, 2H, J=7.7 Hz), 3.32 (d, 2H, J=6.8 Hz), 0.81 (m, 1H), 0.28 (m, 2H), 0.00 (m, 2H)

PD 0296771

mp 266.7-268.9 °C

^{1}H-NMR (400 MHz; DMSO) δ 13.85 (broad s, 1H), 8.99 (s, 1H), 7.87 (dd, 1H, J=7.9, 2.1 Hz), 7.55 (d,2H, J=8.6 Hz), 6.82 (dd, 2H, J=8.7, 2.8 Hz)

PD 0296770

mp 293.2-296.3 °C

^{1}H-NMR (400 MHz; DMSO) δ 14.05 (broad s, 1H), 9.21 (s, 1H), 7.93 (dd, 1H, J=7.8, 2.2 Hz), 7.82 (d,1H, J=1.9 Hz), 7.54 (dd, 1H, J=8.6, 1.9 Hz), 6.82 (dd, 1H, J=8.6, 6.7 Hz)

PD 0296767

mp 249-251 °C

^{1}H-NMR (400 MHz; DMSO) δ 13.99 (broad s, 1H), 9.01 (s, 1H), 7.90 (dd, 1H, J=7.9, 2.3 Hz), 7.58 (d,1H, J=1.6 Hz), 7.42 (dd, 1H, J=8.4, 1.9 Hz), 6.69 (dd, 1H, J=8.4, 6.0 Hz), 2.24 (s, 3H)

PD 298127

mp 127-135 °C

5-chloro-N-cyclopropyl methoxy-3,4-difluoro-2-[4-iodo-2-methyl phenylamino]benzamide

^{1}H NMR (440 MHz; DMSO) δ 11.64 (s, 1H), 8.28 (s, 1H), 7.38 (dd, 1H, J=7.6, 1.7 Hz), 7.31 (d, 1 H, J=1.2 Hz), 7.15 (dd, 1H, J=8.5, 1.7 Hz), 3.35 (d, 2H, J=7.3 Hz), 2.01 (s, 3H), 0.83 (m, 1H), 0.28 (m,2H), 0.01 (m, 2H)

BIOLOGICAL ASSAYS

Example 1

Inhibition of IL-2 Production Induced by Concanavalin A (Con A)

Several of the phenyl amine MEK inhibitors described above have been evaluated in a number of assays which establish their utility in preventing the rejection of transplants in mammals. One such assay measured the ability of a test compound to inhibit the production of IL-2 from T cells (T lymphocytes) present in human peripheral blood mononuclear cells (HPBMC). In this assay, the cells (HPBMC) were prepared by first centrifuging tubes of heparinized blood (obtained from normal healthy volunteers) at 1400 rpm for 10 minutes at room temperature. The interphase containing mostly leukocytes was removed and added to a 50 mL centrifuge tube, and diluted with phosphate buffered saline (PBS) to a volume of 40 mL. The diluted PBS solution was added to a 50 mL centrifuge tube containing 7 mL of Histopague (Sigma, Sp. Gr. 1.077). The mixture was centrifuged at 2200 rpm for 20 minutes at room temperature. The middle layer, comprised mostly of peripheral blood mononuclear cells (PBMC), was removed and added to a clean 50 mL centrifuge tube. These cells were diluted with PBS to a volume of 30 mL, and centrifuged at 1000 rpm for 10 minutes at room temperature. The supernatant was removed, and the remaining cells were washed twice with 30 mL portions of PBS. The PBMC were resuspended in medium (Roswell Park Memorial Institute No. 1640 (RPMI-1640), from Gibco BRL, Gaithersburg, MD), and 10% fetal bovine serum (FBS) culture medium. The cells were adjusted to 2.5×10^6 cells/mL.

The compounds to be tested were prepared by dissolving them in dimethylsulfoxide (DMSO) to a concentration of 30 micromolar. Additional dilutions were made in RPMI-1640, and then in RPMI-1640 containing 1% DMSO so that the final in-well concentration of DMSO was 0.25% in all wells.

Concanavalin A (Con A) was purchased from CalBiochem (Catalog No. 234567). A stock solution was prepared by dissolving 250 mg of Con A in 10 mL of sterile water (25 mg/mL).

The assay was carried out by adding 50 μL of the diluted test compounds to appropriate wells of a plate. To the wells were added 100 μL of the PBMC cell solution (2.5×10^6 cells/mL). The mixtures were pre-incubated for 15 minutes at 37°C, in a 5% carbon dioxide incubator. For the HPBMC assay, 50 μL of the Con A solution (80 μg/mL Con A in RPMI-1640) were added to the appropriate wells. For the HWB assay, 50 μL of a Con A solution (800 μg/mL Con A in RPMI-1640) were added to the appropriate wells. Control wells contained medium plus 50 μL of RPMI-1640. The well plates were incubated for 2 days at 37°C in a 5% carbon dioxide incubator. At the end of Day 2, the plates were centrifuged at 2200 rpm for 5 minutes at 0-4°C. Samples of supernatant (150 μL) were removed from each well and stored at -20°C until analyzed. Each sample was analyzed by an IL-2 ELISA kit (No. D2050 from R & D Systems, Minneapolis, MN) to measure the content of IL-2.

The results of the foregoing assay are shown in Figures 1 and 9. A preferred compound to be used in accordance with this invention is 2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide, also known as PD 184352. Figure 1 shows that no IL-2 is produced by unstimulated cells, but large amounts are produced in the presence of Con A. The Figure shows that PD 184352 causes a dramatic dose dependent inhibition of IL-2 production, and has an IC_{50} of 71 nM.

Figure 9 shows the inhibition of IL-2 production in cells caused by several of the phenyl amine MEK inhibitors of Formulas I and II, compared to known immunosuppressive agents dexamethasone, a steroid, which is 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione, and rolipram, a phosphodiesterase-4 inhibitor which is 4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone. The data establish that the phenyl amine MEK inhibitors are in general very potent in their ability to inhibit IL-2 production.

Example 2

Inhibition of IL-2 Production Induced by Anti-CD3 & Anti-CD28

Stimulation of T cells through direct activation of the T cell receptor is felt to be more representative of physiologic T cell activation than when cells are activated by mitogens, such as Con A. The T cell receptor is a complex, multi-protein receptor comprised in part of a set up proteins collectively called CD3. In order for T cells to produce IL-2, they must also be activated by a co-receptor. The most prominent and best-characterized T cell co-receptor is CD28. Monoclonal antibodies to CD3 and CD28 and be used together to induce release of IL-2.

Anti-CD3 was purchased from BioSource Int. (catalog #AHS2812). A working solution was prepared containing 10 μg/mL of anti-CD3 in PBS. A 100 μL aliquot was added to appropriate wells and incubated for 3 hours at 37°C, and then unbound anti-CD3 was washed off with PBS. Anti-CD28 was purchased from BioSource Int. (catalog #AH0312) and was added as a solution (0.5 μg/mL) to appropriate wells after addition of HPBMC and MEK inhibitor.

HPBMC were prepared as described in Example 1 and stimulated with concentrations of anti-CD3 and anti-CD28 determined from pilot studies to provide a high degree of T cell activation, and hence IL-2 release. After a 2-day culture period in a humidified 37°C incubator containing 5% CO_2 in air, supernatant was collected and assayed for IL-2 as described in Example 1.

The results of the foregoing assay are shown in Figure 2. A preferred compound to be used in accordance with this invention is PD 184352. The Figure shows that no IL-2 is produced by unstimulated cells, but large amounts are produced in the presence of anti-3 plus anti-CD28. The Figure shows that PD 184352 causes a dramatic dose dependent inhibition of IL-2 production, and has an IC_{50} of 47 nM.

Example 3

Inhibition of Interferon-γ Production

The foregoing procedure was followed to evaluate the ability of the phenyl amine MEK inhibitors of Formulas I and II to inhibit the release of interferon gamma (IFN-gamma) from human peripheral blood mononuclear cells (HPBMC) and human whole blood (HWB). The cell samples and compound samples were prepared by the general procedure described above. The assays of the incubated well plates were carried out using an IFN-gamma ELISA kit (No. DIF00 from R & D Systems). The results of the assays are shown in Figures 3 and 10. Figure 3 shows that Con A causes a large production of IFN-gamma, and that such production is totally inhibited by PD 184352 at some concentrations. The Figure shows that the IC_{50} for PD 184352 against IFN-gamma is 148 nM.

Figure 10 shows the dose dependent inhibition of IFN-gamma caused by various phenyl amine MEK inhibitors of Formulas I and II, and the activity of known immunosuppressive agents rolipram and dexamethasone. The data establish that the phenyl amine MEK inhibitors are much more potent that rolipram, and cause almost 100% inhibition at concentrations of 1 μM or higher. The ability of the MEK inhibitors of Formulas I and II to inhibit IFN-gamma production establishes that they can be used for the prophylaxis of transplants of organs, limbs, cells, and tissues in mammals.

Example 4

Human Mixed Lymphocyte Reaction

Several of the MEK inhibitors which are to be used in the method of this invention have been evaluated in an in vitro test in which lymphocytes (or leukocytes) from one donor (eg, the potential recipient of a transplant) are cultured in the presence of leukocytes from another donor (eg, the potential transplant donor, generally a living related donor, not cadaveric donors). This test measures the degree of histoincompatibility. The assay is a mixed lymphocyte (or leukocyte) reaction, and is referred to as the "MLR". In this assay, inhibition of tritiated thymidine (^{3}H-TDR) incorporation is measured. Tritiated thymidine was supplied from Amersham (Catalog No. TRK.758, 250 μCi). The commercial

product was diluted in RPMI-1640 in a 50 mL conical centrifuge tube to provide a working stock solution of 5-10 μCi/mL. Cells and test compounds were prepared as described above. The compounds and cells were incubated at 37°C in a 5% carbon dioxide incubator. On Day 6, each well of the assay plate was labeled with the ^{3}H-TDR working stock solution (total of 0.1 - 0.5 μCi per well). The plates were incubated an additional 6 hours following labeling. The plate samples were harvested using a multichannel harvester, and the radioactivity of each sample was counted using a betaplate Wallace 1205 counter.

Figure 4 shows the activity of PD 184352 in the human MLR assay. The activity is measured as counts per minute (CPM) of tritiated thymidine (^{3}H-TDR) uptake. The Figure shows that untreated MLR values are in excess of 4500 CPM, whereas the test compound causes a dose dependent inhibition of ^{3}H-TDR uptake, with almost total inhibition occurring at 10 μM. The IC_{50} for PD 184352 was established as 186 nM.

Figure 11 shows the activity of several phenyl amine MEK inhibitors in the MLR assay, compared to dexamethasone.

The data presented in Figures 4 and 11 further establish that the selective MEK inhibitors of Formulas I and II are useful for preventing the rejection of transplanted organs, tissues, cells, and limbs in mammals.

Example 5

Inhibition of T-Cell Proliferation induced by Con A

Another measure of immunosuppressive activity is a compound's ability to block the growth of T cells. Uncontrolled proliferation of T cells leads to rejection of transplanted organs, tissues, cells, and limbs in mammals. Immunological studies have established that cyclosporine A blocks activation of T cells, and that this is partly the result of inhibition of the synthesis of interleukin-2, the main growth factor for T cells. The assay was carried out by following the general procedure described above for preparing cells and test compounds, and ^{3}H-TDR inhibition was measured. Con A was used to induce T-cell proliferation.

Figure 5 shows the degree to which PD 184352 inhibits T-cell proliferation. Namely, the compound causes about 50% inhibition of the Con A

induced proliferation at the lowest dose tested (0.12 μM), and causes almost total inhibition at the highest dose tested (10.0 μM). The IC_{50} for the compound was determined to be 340 nM.

Figure 12 shows that all of the phenyl amine MEK inhibitors that were tested caused a dramatic and dose dependent inhibition of T-cell proliferation.

Example 6

Inhibition of T-Cell Proliferation induced by Phytohemagglutinin (PHA)

The T-cell inhibition study was carried out using the agent PHA to induce the proliferation. Figure 6 shows the effects of PD 184352. In this study, the test compound failed to cause inhibition at the low dose (0.12 μM), but caused a measurable inhibition at all other doses, with almost total inhibition at the high dose (10 μM). The IC_{50} was determined to be 1.9 μM in this assay. The data further establish the ability of the phenyl amine MEK inhibitor to inhibit T-cell proliferation, and thereby to be useful in the prophylaxis of transplant rejections in mammals.

Example 7

Toxicity Assay

As noted above, the MEK inhibitors to be used in the method of this invention are potent inhibitors of transplant rejection, while at the same time have little or no toxicity, a feature which severely limits the clinical usefulness of commercial immunosuppressive agents. The toxic effects of the compounds were evaluated in an assay using MTT, which is a chemical substance known as 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide. MTT changes color when it is activated by a cell, and that color change can be measured by routine methods. Only living cells can change the color of MTT. For this assay, living U-937 cells were obtained from American Type Culture Collection (Rockville, MD). PD 184352 was added to the cells in plate wells, and the cells were incubated as described above. Following the incubation period, the color change of MTT was measured using a spectrophotometer. Figure 7 shows that PD 184352 caused no toxicity at concentrations below 33 μM, and caused only

slight color change even at concentrations as high as 100 μM. The dose of PD 184352 required to cause cell death of one-half of the cells (the TC_{50}) was thus determined to be greater than 100 μM. These data establish that the phenyl amine MEK inhibitors are essentially devoid of any toxic effects in this assay.

Figure 13 shows the toxicity of several of the phenyl amine MEK inhibitors when evaluated in the MTT assay. The data establish that all of the compounds evaluated have a very favorable therapeutic index, ie, biological efficacy for prophylaxis of transplant rejection vs toxicity. Thus, the compounds will find widespread use in the clinical setting for preventing and controlling transplant rejection in mammals.

Figure 8 shows the relative activities of several of the phenyl amine MEK inhibitors of Formulas I and II, compared with the activities of rolipram and dexamethasone, in a number of the assays described above. The Figure establishes that the phenyl amine MEK inhibitors are, in general, as active as or more active than the known agents when evaluated in standard assays which establish utility of compounds in the prophylaxis of transplant rejections in mammals.

Much of the foregoing data is summarized below in Pharmacological Table 1. The Table presents the in vitro effects of several compounds to be used in the method of this invention, together with several comparator immunosuppressive agents, on human leukocytes. The data are concentrations of test compounds required to cause a 50 percent inhibition of the measured parameter (the IC_{50}), except in the case of the toxicity data, which is presented as TC_{50} (concentration required to produce toxicity in 50 percent of the cells). In the Table, "APK" refers to activity of compounds in a cascade assay, wherein a compound inhibits a MEK enzyme, thereby preventing phosphorylation of another enzyme, namely a MAP (mitogen activated protein) kinase, which otherwise would cause phosphorylation of a substrate, in this assay said substrate being myelin basic protein The comparator agent U0126 (in Pharmacological Table 1) is 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadiene, an immunosuppressive compound described in US Patent No. 2,779,780.

PHARMACOLOGICAL TABLE 1

MEK Inhibitors: In Vitro Effects on Human Leukocytes
(All data are mean (*) IC_{50s} or % inhibition at the concentration given, except toxicity data (MTT) which are $TC_{50}S$)

	APK IC_{50} (nM)	Human IL-2 (μM)	IFN-gamma (μM)	U937 MTT TC_{50} (μM) or (% dead)	^{3}H-TDR PHA (μM)	^{3}H-TDR MLR (μM)	^{3}H-TDR Con A (μM)
171984-0000	3.0	0.019	*0.034	50.6	*2.4	0.35	*0.19
177098-0000	14.0	0.006	*0.076	*29.9	*NJ	*NJ	*3.9
177168-0000	18.0	0.052	*0.17	*13.9	*2.5	0.69	*0.52
180841-0000	4.4	*0.11	*0.21	*5.8	*ND	*NJ	*ND
184161-0000	1.6	*0.19	*0.15	*12.6	*1.8	0.53	*0.61
184352-0000	1.3	0.068	*0.14	>100 (6%)	*4.5	0.64	*0.52
184386-0000	1.4	0.039	*0.040	61	*4.0	0.41	*0.31
185625-0000	5.1	0.071	*0.12	*12.4	*NJ	*0.39	*4.0
185848-0000	1.0	0.018	*0.024	38.1	*NJ	*0.51	*NJ
188563-0000	1.3	0.013	*0.15	40	*NJ	*0.17	*NJ
198306-0000	8.0	0.037	*0.15	13.1	*1.40	*1.8	*1.9
203311-0000	--	0.032	*0.10	*32.2	*ND	*0.076	*ND

ND = not determined. NJ = no judgment: Studies indeterminant or incomplete.

PHARMACOLOGICAL TABLE 1 (cont)

MEK Inhibitors: In Vitro Effects on Human Leukocytes
(All data are mean (*) IC_{50s} or % inhibition at the concentration given, except toxicity data (MTT) which are TC_{50s})

	APK IC_{50} (nM)	Human IL-2 (μM)	IFN-gamma (μM)	U937 MTT TC_{50} (μM) or (% dead)	^{3}H-TDR PHA (μM)	^{3}H-TDR MLR (μM)	^{3}H-TDR Con A (μM)
STANDARDS							
98059-0000	>1000	*7.4	*5.8	>100 (0%)	*>10	*5.1	*>10
U0126 (PD 199601)	--	0.077	*0.25	>100 (0%)	*NJ	*0.83	*NJ
Rolipram	--	0.094	*0.65	*ND	*>10	*3.5	*NJ
Dexamethasone	--	*0.005	*0.005	>100 (0%)	*>10	*0.01	*<0.041

The foregoing extensive biological evaluations clearly establish the selective MEK inhibitors described above, especially the phenyl amines of Formulas I and II, are well-suited to the prophylaxis of transplant rejections in mammals, preferably humans. Like other immunosuppressive agents, the MEK inhibitors can be used in combination with other such agents for even better

results. For example, the MEK inhibitors can be combined clinically with agents such as cyclosporine A and FK 506, another well-known immunosuppressive agent. The agents can be combined into the same formulation, but are more typically administered in their individual formulated doses, and normally at the dose levels routinely used for the individual agents when used alone; however, lower or higher doses can be used if desired. The individual agents can be packaged together for convenience of the medical practitioner, for example in a kit or the like.

Example 8

The selective MEK inhibitors to be used in the method of this invention will additionally be evaluated in in vivo assays that establish their ability to prevent and control transplant rejections. A typical in vivo assay is an allogeneic mouse ear-heart model using neonatal or newborn mouse hearts. Mice of the BL/6 to C3H strain will be used as test animals. Ten mice will be treated with a MEK inhibitor. Three vehicle control allografts will be included, as well as three isografts, as control animals. Mice will be dosed at 50 mg/kg twice each day, until grafts are rejected, or until there is evidence of a definite anti-rejection effect. The MEK inhibitor being evaluated will be dissolved in a dosing solution which is 10% ethanol, 10% Cremophor EL (Sigma, Cat. No. C-5135), and 80% water (v/v/v). The test animals are dosed orally using a tuberculin syringe and a mouse oral gavage tube. The dosing ratio is 0.1 mL of solution per each 20 g of mouse weight. The MEK inhibitor (300 mg) to be tested is placed in a 50 mL conical tube, and 3.0 mL of ethanol is added. The tube is capped to retard evaporation and vortexed to facilitate dissolution. The Cremophor EL (3.0 mL) is added, followed by the addition of 24.0 mL of water. The 30 mL dosing solution is vortexed, and stored at 5°C until used.

If any grafts are rejected at any time during the study, the animal is sacrificed by dry ice (CO_2) asphyxiation as soon as graft rejection is determined. All specimens are obtained immediately after sacrificing the animals, and placed in 10-20 mL of buffered formalin. If all allografts survive to the end of the study, one-half are placed in the buffered formalin, and the other half are frozen for subsequent analysis. The following tissues are collected for histopathology and

phospho-ERK analysis: ear bearing the allograft (or isograft); ipsilateral cervical lymph nodes; contralateral cervical lymph nodes; the spleen; and heparinized blood collected by cardiac puncture for determination of drug concentration. If transplants are still surviving on Day 50, the study is terminated, and the above noted specimens are collected and analyzed.

The method of this invention provides for both prophylaxis and maintenance of patients who have undergone a transplant or are scheduled to undergo a transplant. Evaluation of one MEK inhibitor, 2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide (PD 198306)) was performed using the aforementioned protocol, but no enhancement of graft survival was observed (data not shown). This may be the result of any or a combination of several factors, among which is insufficient exposure of target cells to an adequate and sustained concentration of the MEK inhibitor. Survival time of isografts in mice treated with PD 198306 was somewhat shortened, which may suggest that MEK inhibitors might be more efficacious for graft maintenance.

D. Other Embodiments

From the above disclosure and examples, and from the claims below, the essential features of the invention are readily apparent. The scope of the invention also encompasses various modifications and adaptations within the knowledge of a person of ordinary skill. Examples include a disclosed compound modified by addition or removal of a protecting group, or an ester, pharmaceutical salt, hydrate, acid, or amide of a disclosed compound. Publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

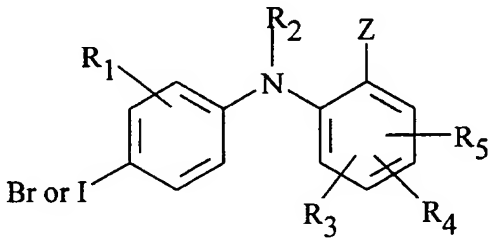
CLAIMS

1. A method for preventing and controlling the rejection, in a patient, of a transplanted organ, cell, tissue, or limb, said method comprising administering to the patient who has undergone a transplant, or who is scheduled to undergo a transplant, an effective immunosuppressive amount of a MEK inhibitor.

2. A method according to Claim 1 wherein the MEK inhibitor administered is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran.

3. The method according to Claim 1, wherein said MEK inhibitor is a selective MEK 1 or MEK 2 inhibitor.

4. The method according to Claim 1 wherein the MEK inhibitor is a compound of Formula I



I

wherein:

R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_2 is hydrogen;

R_3, R_4, and R_5 independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or -(O or NH)$_m$-$(CH_2)_n$-R_9, where R_9 is hydrogen, hydroxy, COOH, or $NR_{10}R_{11}$;

n is 0-4;

m is 0 or 1;

R_{10} and R_{11} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7;

R_6 and R_7 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, (CO)-C_1-C_8 alkyl, aryl, heteroaryl, C_3-C_{10} cycloalkyl, or C_3-C_{10} (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R_6 and R_7 together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl; and wherein any of the foregoing alkyl, alkenyl, aryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl,phenoxy, C_3-C_5 heteroaryl, or C_3-C_5 heteroaryloxy;

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

5. The method according to Claim 4 wherein the MEK inhibitor is a compound selected from:

[4-Chloro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine;

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine;

[4-nitro-2-(1H-tetrazol-5-yl)-phenyl-(4-iodo-2-methyl-phenyl)-amine;

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;

4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;

5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;

2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide;

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide;

5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanone;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;

N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone;

5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;

N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol;

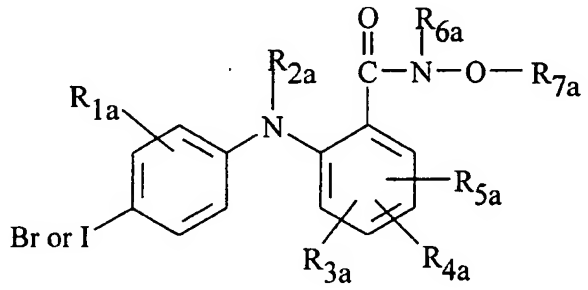
[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol; and

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

6. The method of claim 4, wherein the MEK inhibitor is a compound of Formula (I) wherein (a) R_1 is hydrogen, methyl, methoxy, fluoro, chloro, or bromo; (b) R_2 is hydrogen; (c) R_3, R_4, and R_5 independently are hydrogen, fluoro, chloro, bromo, iodo, methyl, methoxy, or nitro; (d) R_{10} and R_{11} independently are hydrogen or methyl; (e) Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7; R_6 and R_7 independently are hydrogen, C_{1-4} alkyl, heteroaryl, or C_{3-5} cycloalkyl optionally containing one or two heteroatoms selected from O, S, or NH; or R_6 and R_7 together with the nitrogen to which they are attached complete a 5-6 member cyclic ring optionally containing 1 or 2 additional heteroatoms selected from O, NH or N-alkyl; and wherein any of the foregoing alkyl or aryl groups can be unsubstituted or substituted by halo, hydroxy, methoxy, ethoxy, or heteroaryloxy; (f) Z is $COOR_7$; (g) R7 is H, pentafluorophenyl, or tetrazolyl; (h) R_3, R_4, and R_5 are independently H, fluoro, or chloro; (i) R_4 is fluoro; (j) two of R_3, R_4, and R_5 are fluoro; or (k) combinations of the above.

7. The method of claim 6, wherein the MEK inhibitor is a compound of Formula (I) wherein: Z is $COOR_7$; R_7 is H, pentafluorophenyl, or tetrazolyl; R_3 and R_5 are independently H, fluoro, or chloro; and R_4 is fluoro.

8. A method according to claim 1, where the MEK inhibitor is a compound of Formula II



II

wherein:

R_{1a} is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_{2a} is hydrogen;

R_{3a}, R_{4a}, and R_{5a} independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or (O or NH)$_m$-$(CH_2)_n$-R_{9a}, where R_{9a} is hydrogen, hydroxy, CO_2H or $NR_{10a}R_{11a}$.

n is 0-4;

m is 0 or 1;

R_{10a} and R_{11a} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

R_{6a} is hydrogen, C_1-C_8 alkyl, (CO)-C_1-C_8 alkyl, aryl, aralkyl, or C_3-C_{10} cycloalkyl;

R_{7a} is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{10} (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a});

and wherein any of the foregoing alkyl, alkenyl, aryl, heteroaryl, heterocyclic, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, C_1-C_6 alkoxy, amino, nitro, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino, C_3-C_6 cycloalkyl, phenyl, phenoxy, C_3-C_5 heteroaryl or heterocyclic radical, or C_3-C_5 heteroaryloxy or heterocyclic radical-oxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or $NR_{10a}R_{11a}$;

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

9. The method of Claim 8, comprising a MEK inhibitor having a structure of Formula (II) wherein: (a) R_{1a} is H, methyl, fluoro, or chloro; (b) R_{2a} is H; R_{3a}, R_{4a}, and R_{5a} are each H, Cl, nitro, or F; (c) R_{6a} is H; (d) R_{7a} is methyl, ethyl, 2-propenyl, propyl, butyl, pentyl, hexyl, cyclopropylmethyl, cyclobutyl methyl, cyclopropylmethyl, or cyclopropylethyl; and (e) the 4' position is I, rather than Br.

10. The method of claim 9, comprising a MEK inhibitor having a structure of Formula (II) wherein: R_{4a} is F at the 4 position, para to the CO-N-R_{6a}-OR_{7a} group and meta to the bridging nitrogen; at least one of R_{3a} and R_{5a} is F or Cl; and R_{1a} is methyl or chloro.

11. The method of Claim 8, comprising a MEK inhibitor having a formula selected from:

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide;

5-Bromo-3-4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-ynyloxy)-benzamide;

5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide;

4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methyl-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide;

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide; and

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide.

12. The method of claim 1, comprising a MEK inhibitor having a structure selected from:

2-(2-chloro-4-iodophenylamino)-5-chloro-N-cyclopropylmethoxy -3,4-difluorobenzamide (PD 297189); 2-(4-iodophenylamino)-N-cyclopropylmethoxy-5-chloro-3,4-difluorobenzamide (PD 297190); 2-(4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296771); 2-(2-chloro-4-iodophenylamino)-5-chloro-3,4-difluorobenzoic acid (PD 296770); 5-chloro-3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzoic acid (PD 296767); and 5-chloro-N-cyclopropylmethoxy -3,4-difluoro-2-(4-iodo-2-methylphenylamino)-benzamide (PD 298127).

13. A method for preventing and controlling the rejection in a patient of a transplanted organ, cell, tissue or limb, said method comprising the step of administering to the patient who has undergone a transplant, or who is scheduled to undergo a transplant, an effective immunosuppressive amount of a compound selected from:

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide (PD184352);

2-(2-Methyl-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD170611);

2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD171984);

2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD177168);

2-(2-Methyl-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluoro-5-bromobenzamide (PD 180841);

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide (PD 184161);

2-(2-Chloro-4-iodophenylamino)-N-hydroxy-3,4-difluoro-5-bromobenzamide (PD184386);

2-(2-Chloro-4-iodophenylamino)-N-cyclobutylmethoxy-3,4-difluorobenzamide (PD 185625);

2-(2-Chloro-4-iodophenylamino)-N-hydroxy-4-fluorobenzamide (PD 185848);

2-(2-Methyl-4-iodophenylamino)-N-hydroxy-3,4-difluorobenzamide(PD 188563);

2-(2-Methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide (PD 198306); and

2-(2-Chloro-4-iodophenylamino)-N-cyclopropylmethoxy-4-fluorobenzamide (PD 203311).

14. A method for the prophylaxis or maintenance of transplant rejection in a mammal comprising administering to a patient in need of prophylaxis or maintenance an effective amount of 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide.

15. A method for the prophylaxis or maintenance of transplant rejection in a mammal comprising administering to a patient in need of prophylaxis or maintenance an effective amount of 2-(2-methyl-4-iodophenylamino)-N-cyclopropylmethoxy-3,4,5-trifluorobenzamide.

FIG. 1 PD 184352 INHIBITION OF IL-2 PRODUCTION INDUCED BY Con A

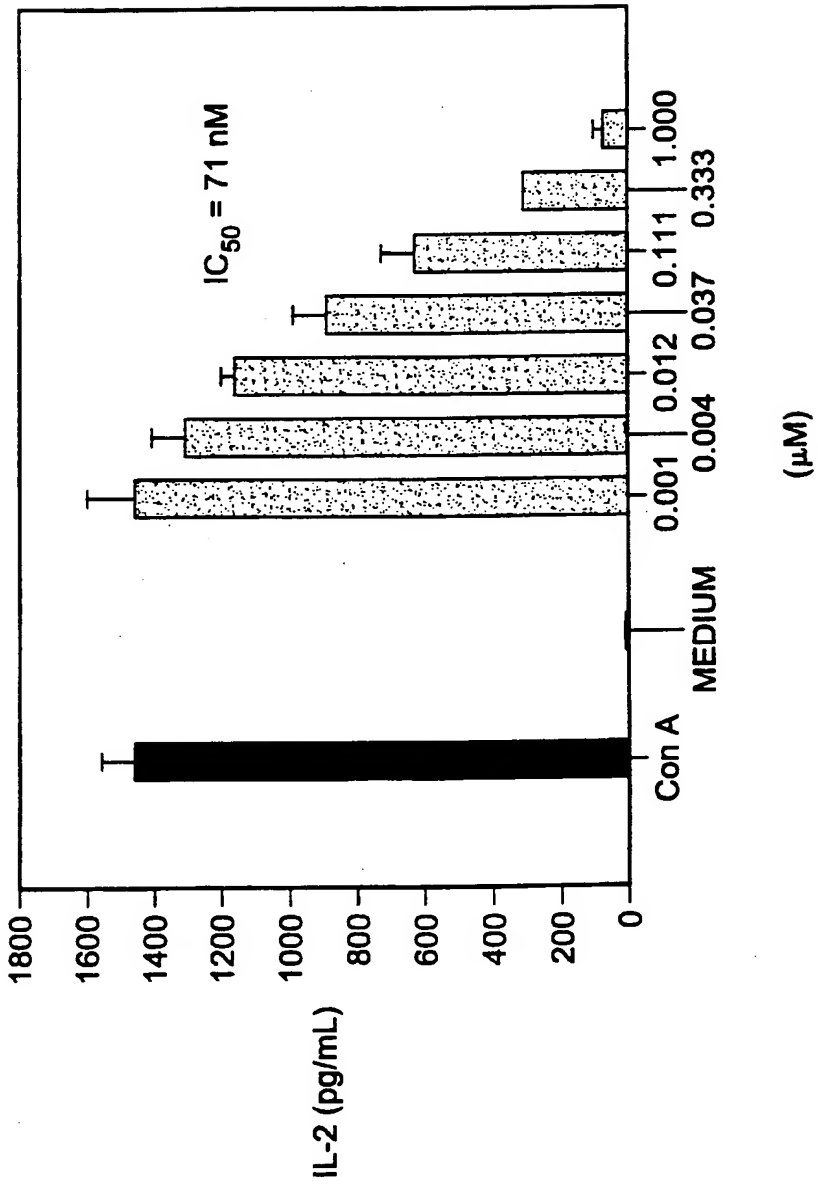


FIG. 2 PD 184352 INHIBITION OF IL-2 PRODUCTION INDUCED BY ANTI-CD3 AND ANTI-CD28 CO-STIMULATION

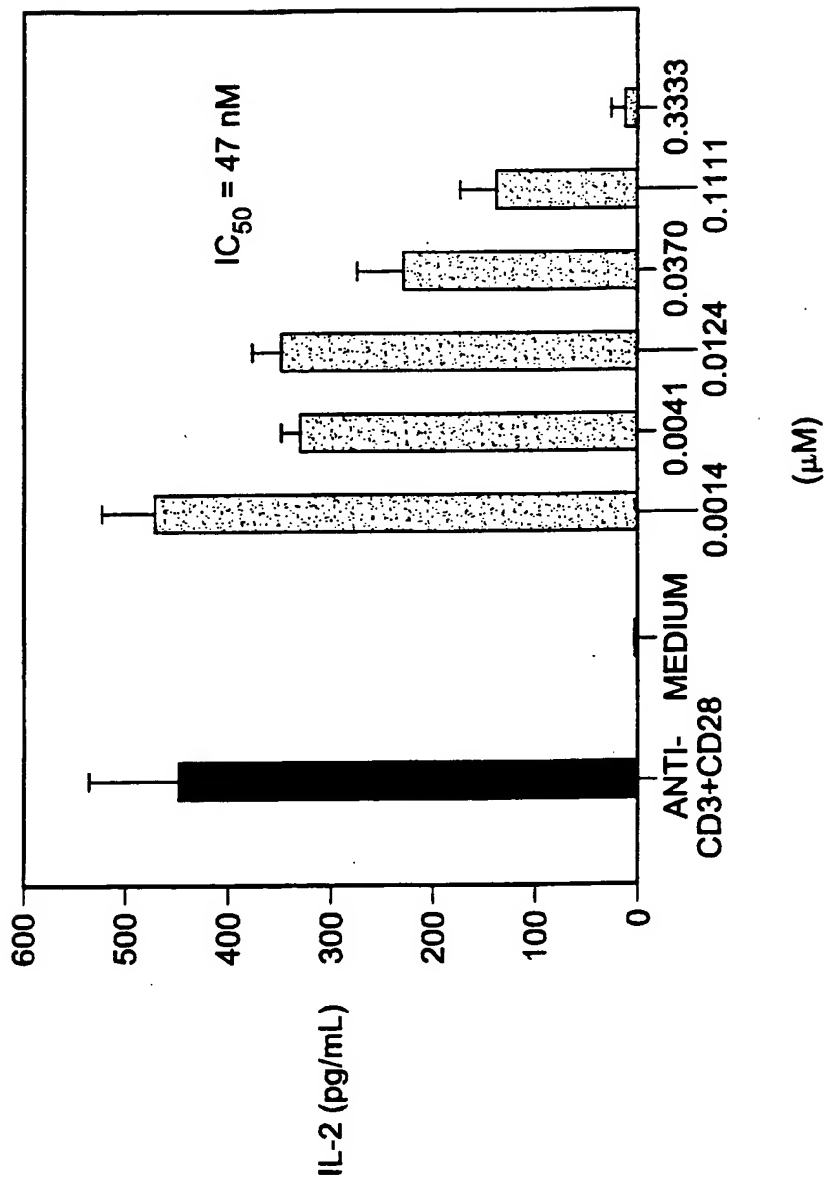


FIG. 3 PD 184352 INHIBITION OF INTERFERON-GAMMA PRODUCTION

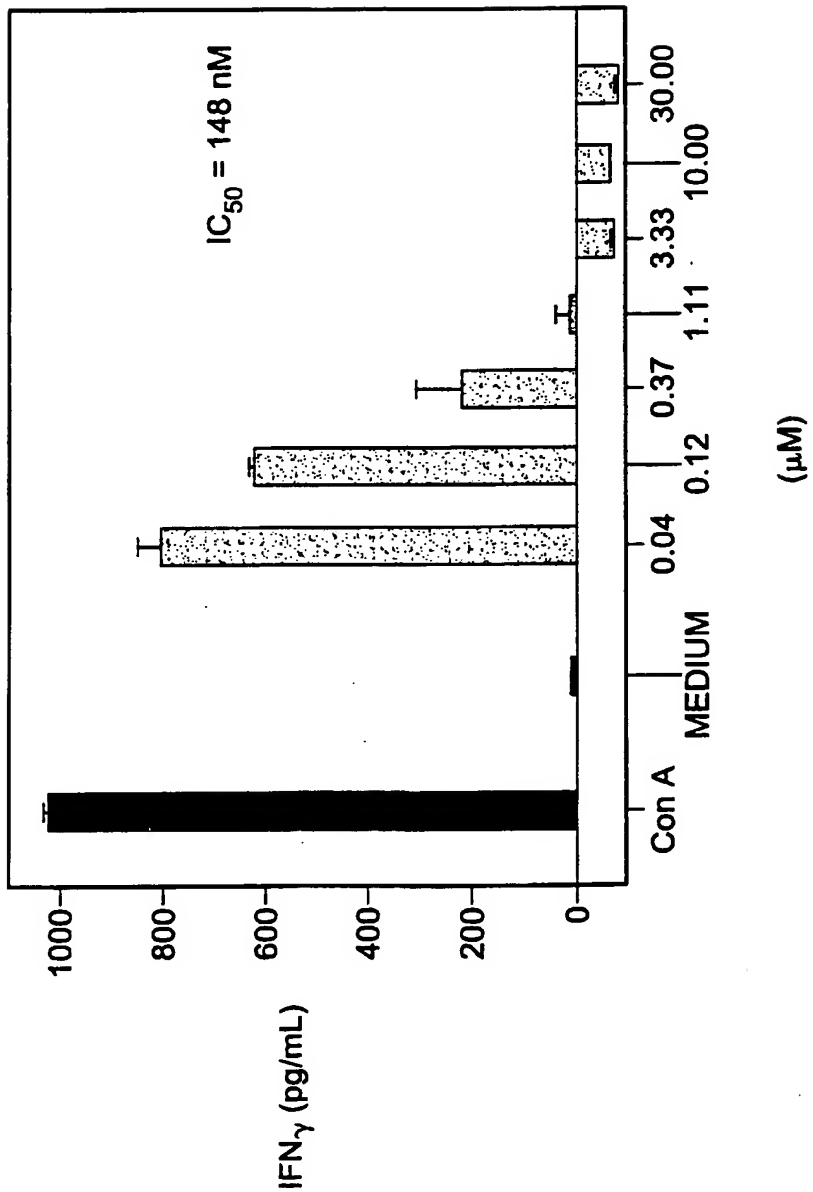


FIG. 4 PD 184352 SUPPRESSES THE HUMAN MLR

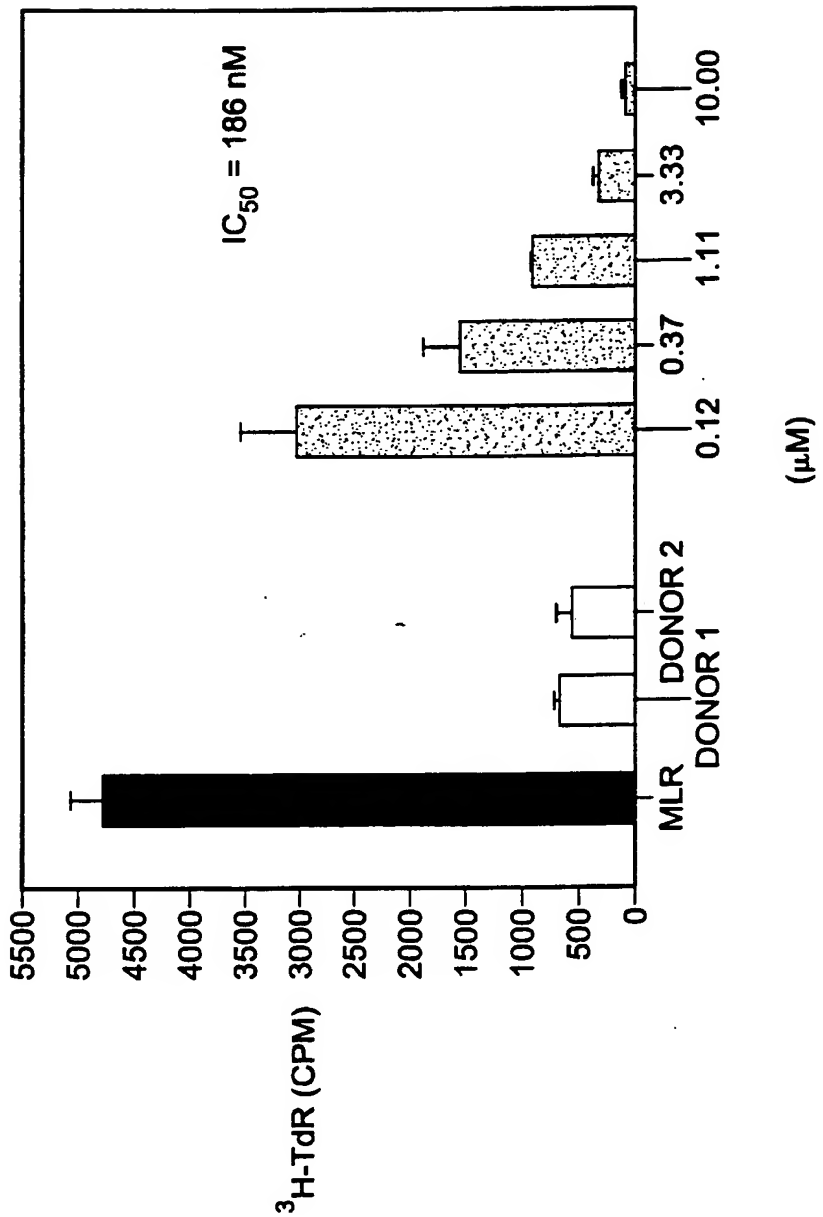


FIG. 5 PD 184352 INHIBITS CONCANAVALIN A (Con A)-INDUCED T CELL PROLIFERATION

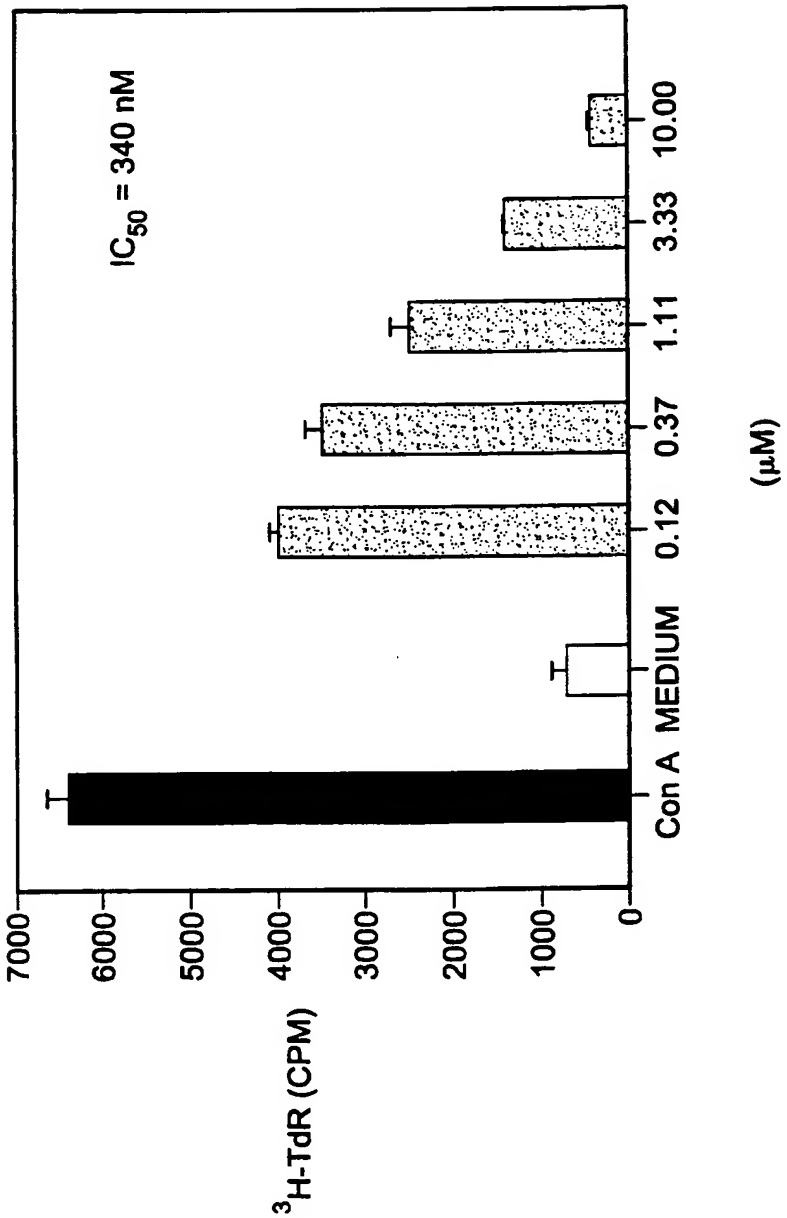


FIG. 6 PD 184352 INHIBITS PHA-INDUCED T CELL PROLIFERATION

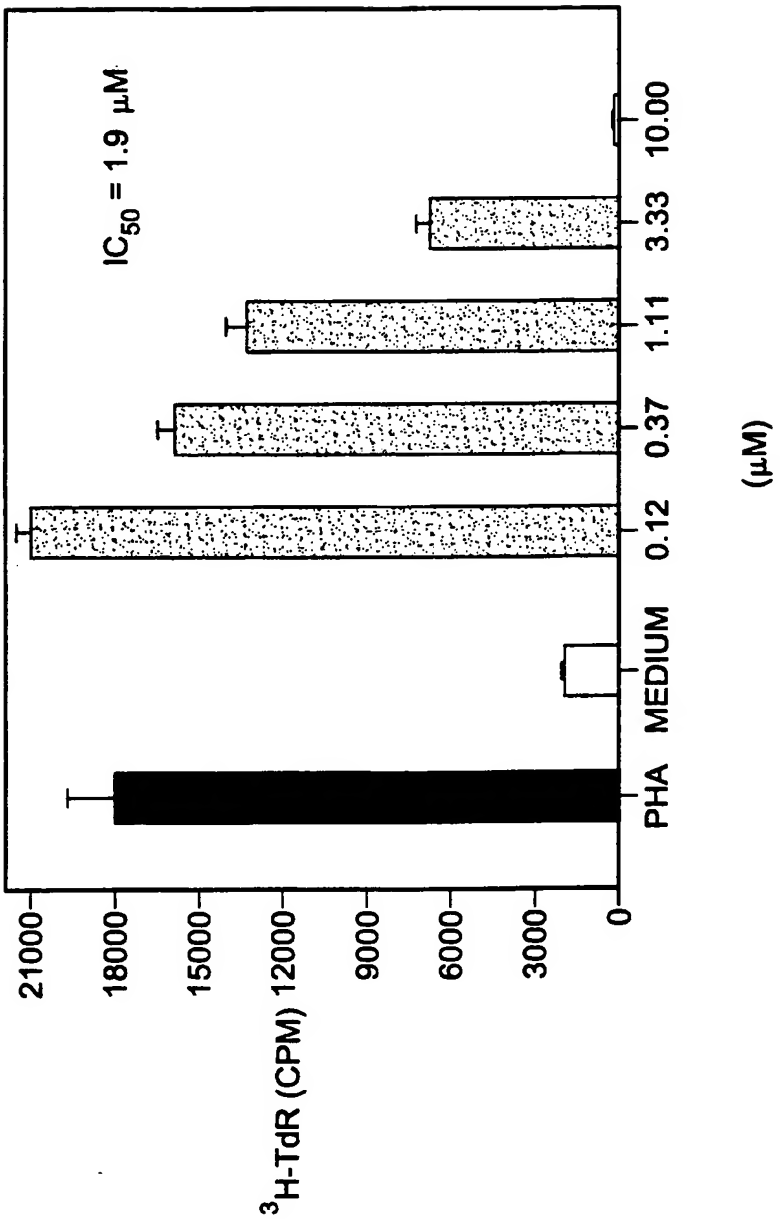


FIG. 7 LACK OF TOXICITY OF PD 184352 FOR U-937 CELLS

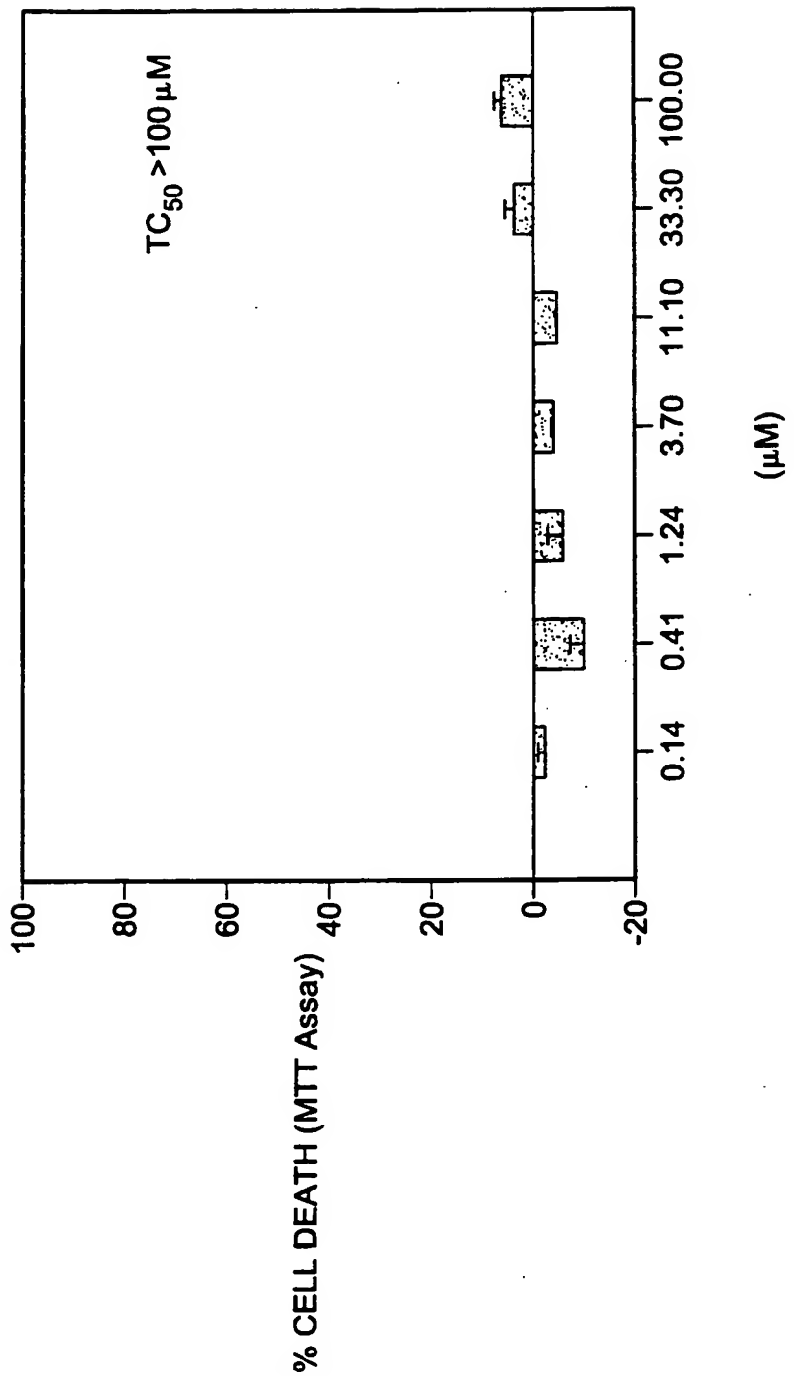


FIG. 8 MEK INHIBITORS: IC_{50}s AND TC_{50}

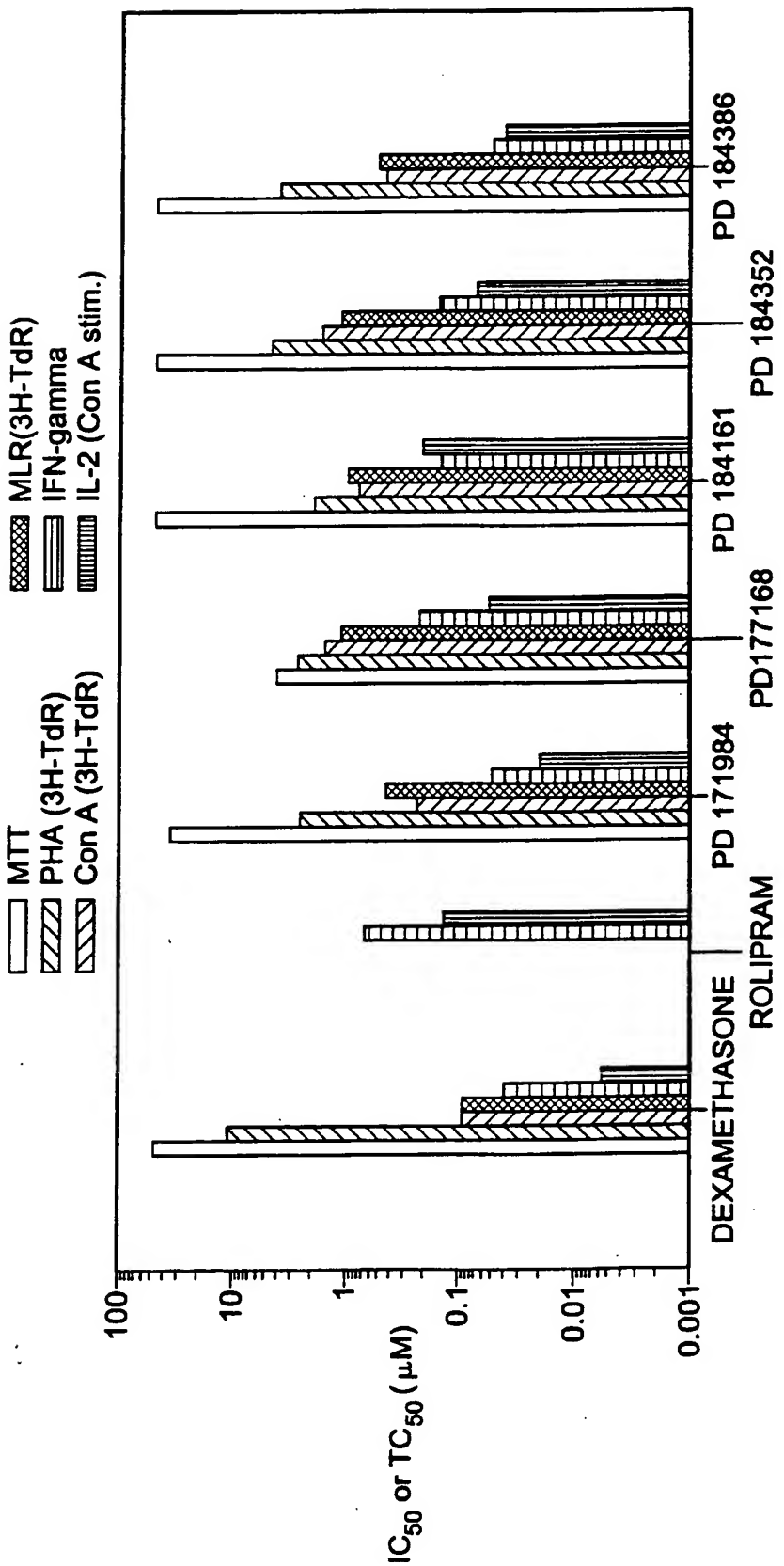


FIG. 9 MEK INHIBITORS SUPPRESS PRODUCTION OF IL-2

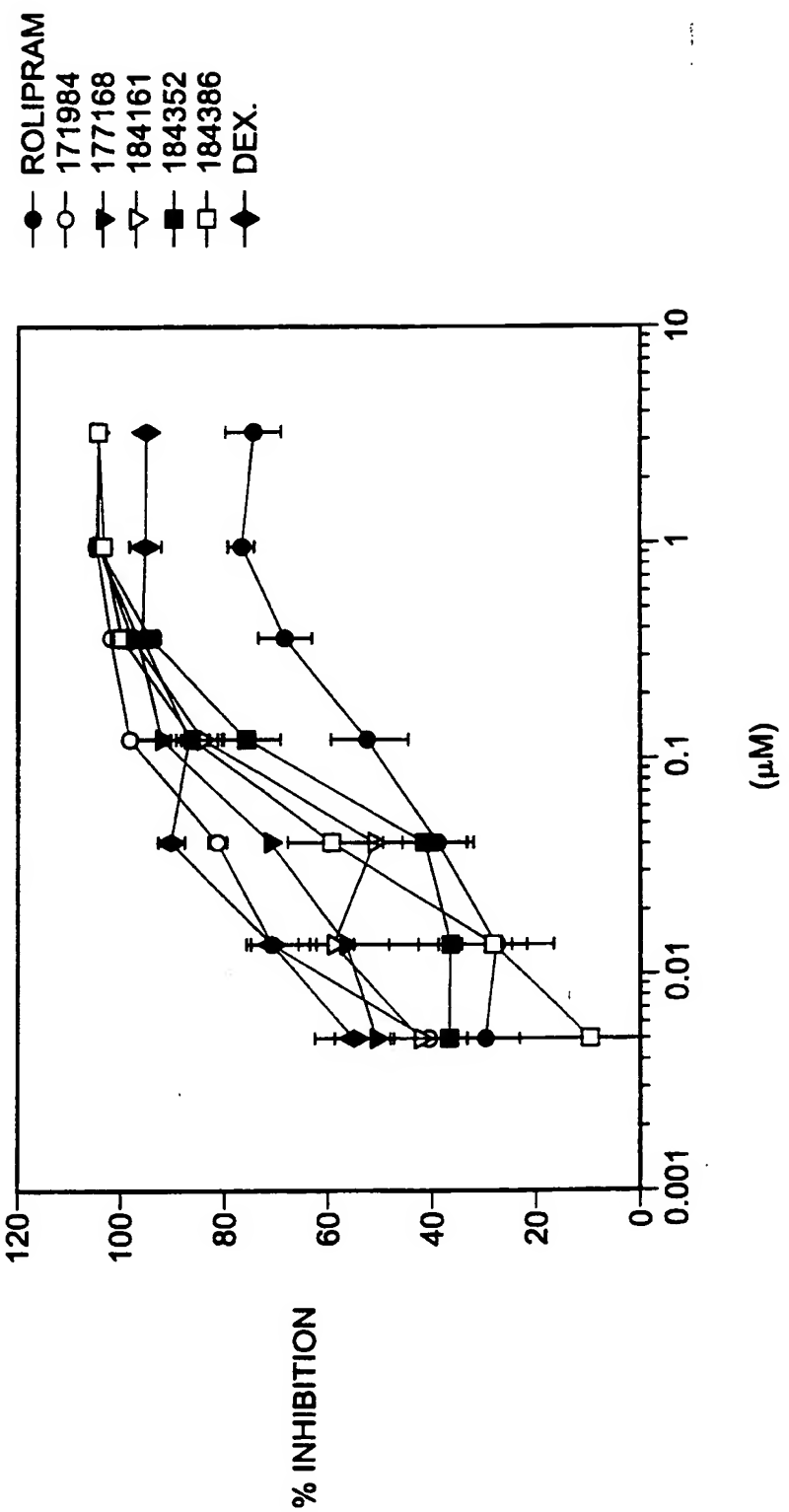


FIG. 10 MEK INHIBITORS SUPPRESS PRODUCTION OF IFN$_\gamma$

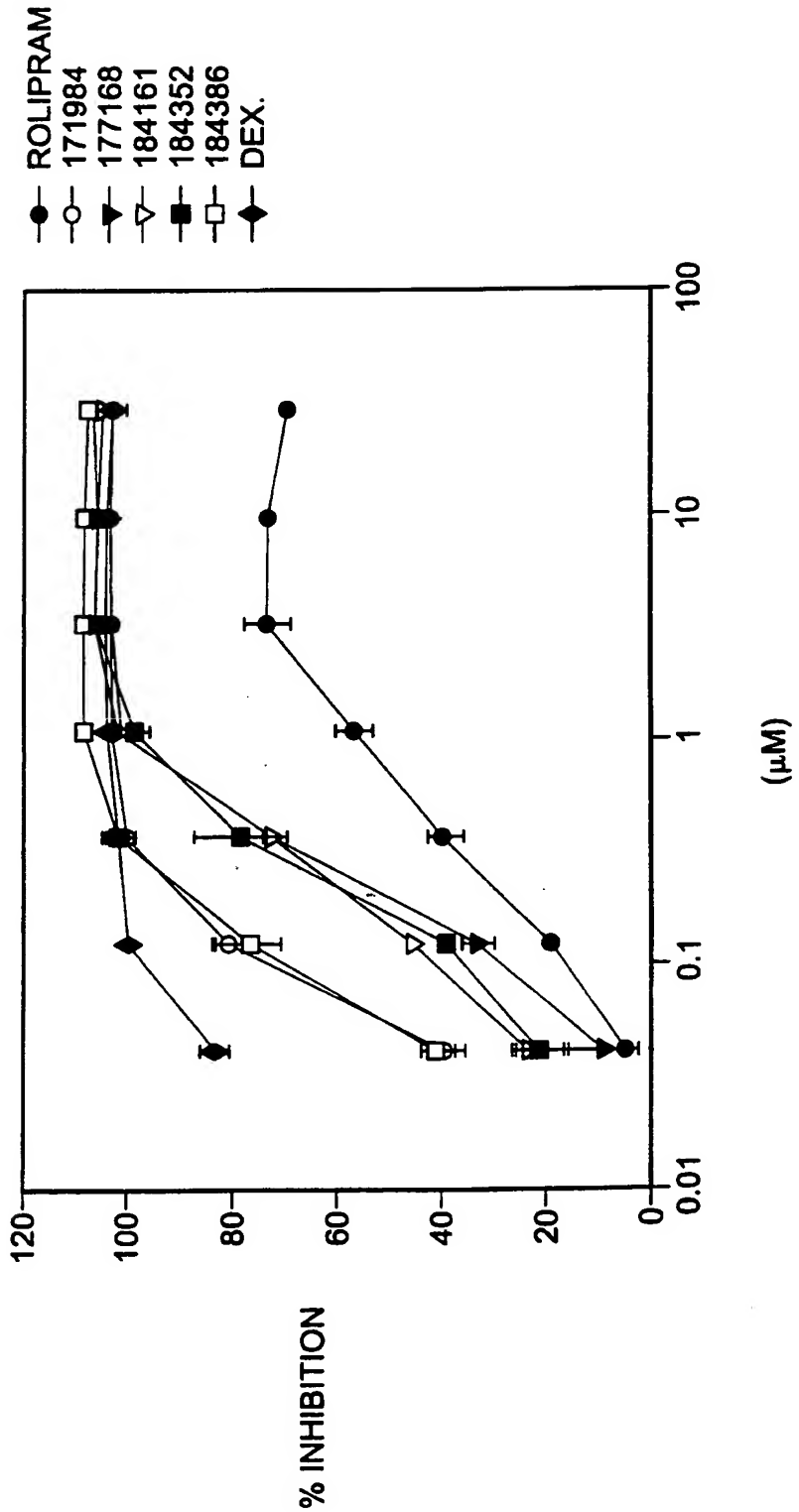


FIG. 11A MEK INHIBITORS SUPPRESS THE HUMAN MLR

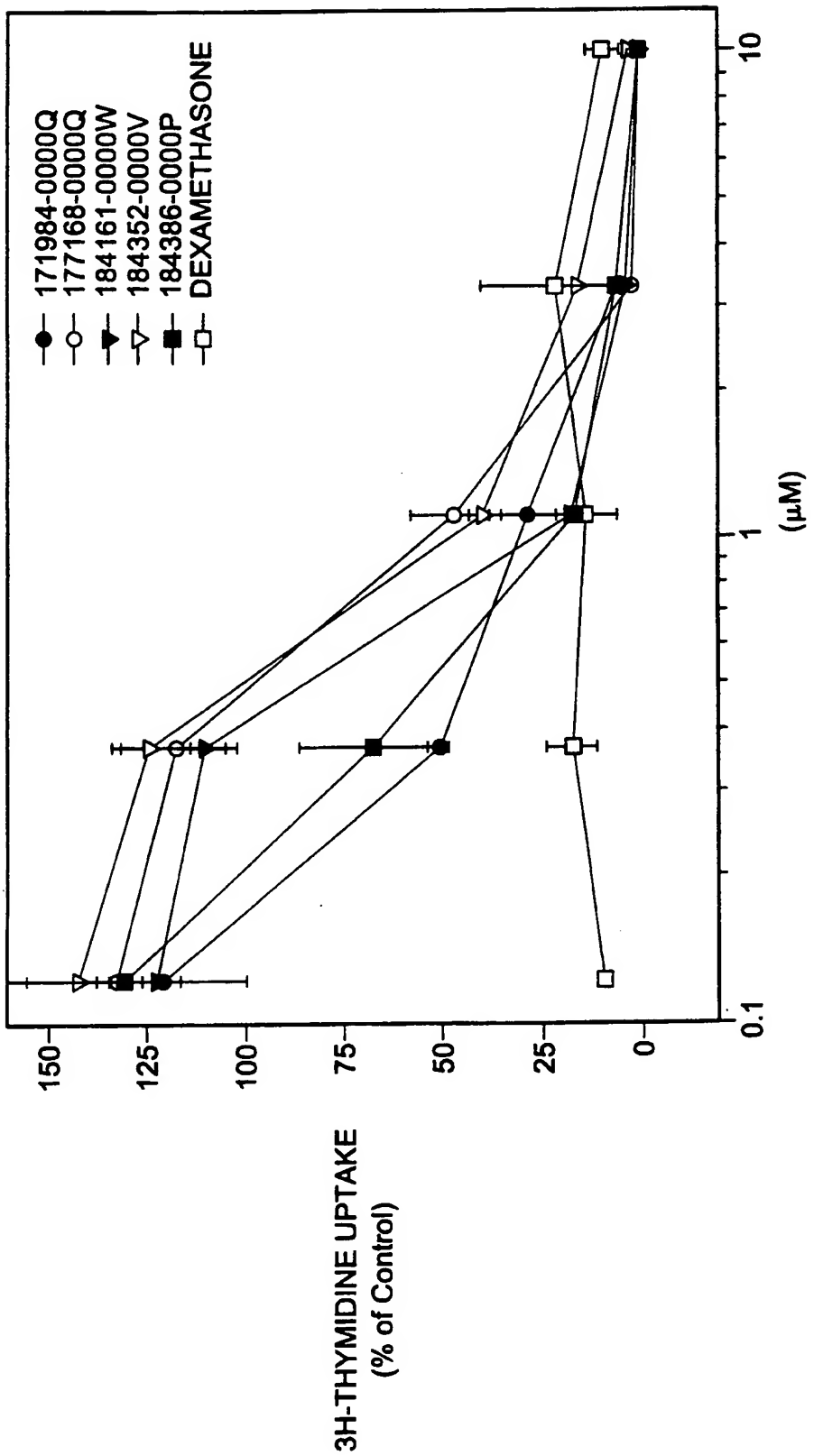


FIG. 11B MEK INHIBITORS SUPPRESS THE HUMAN MLR

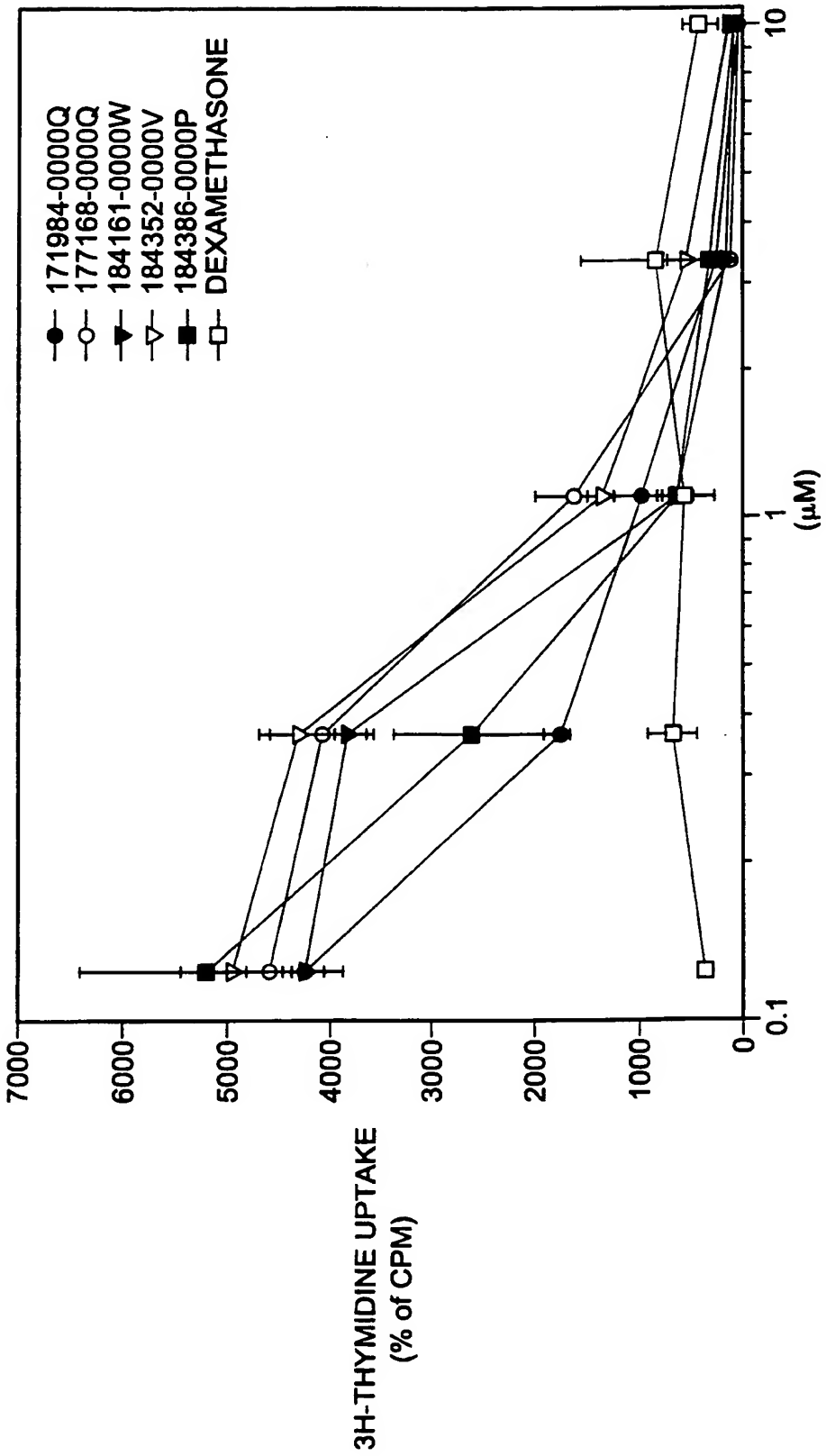


FIG. 12A MEK INHIBITORS SUPPRESS HUMAN T CELL PROLIFERATION

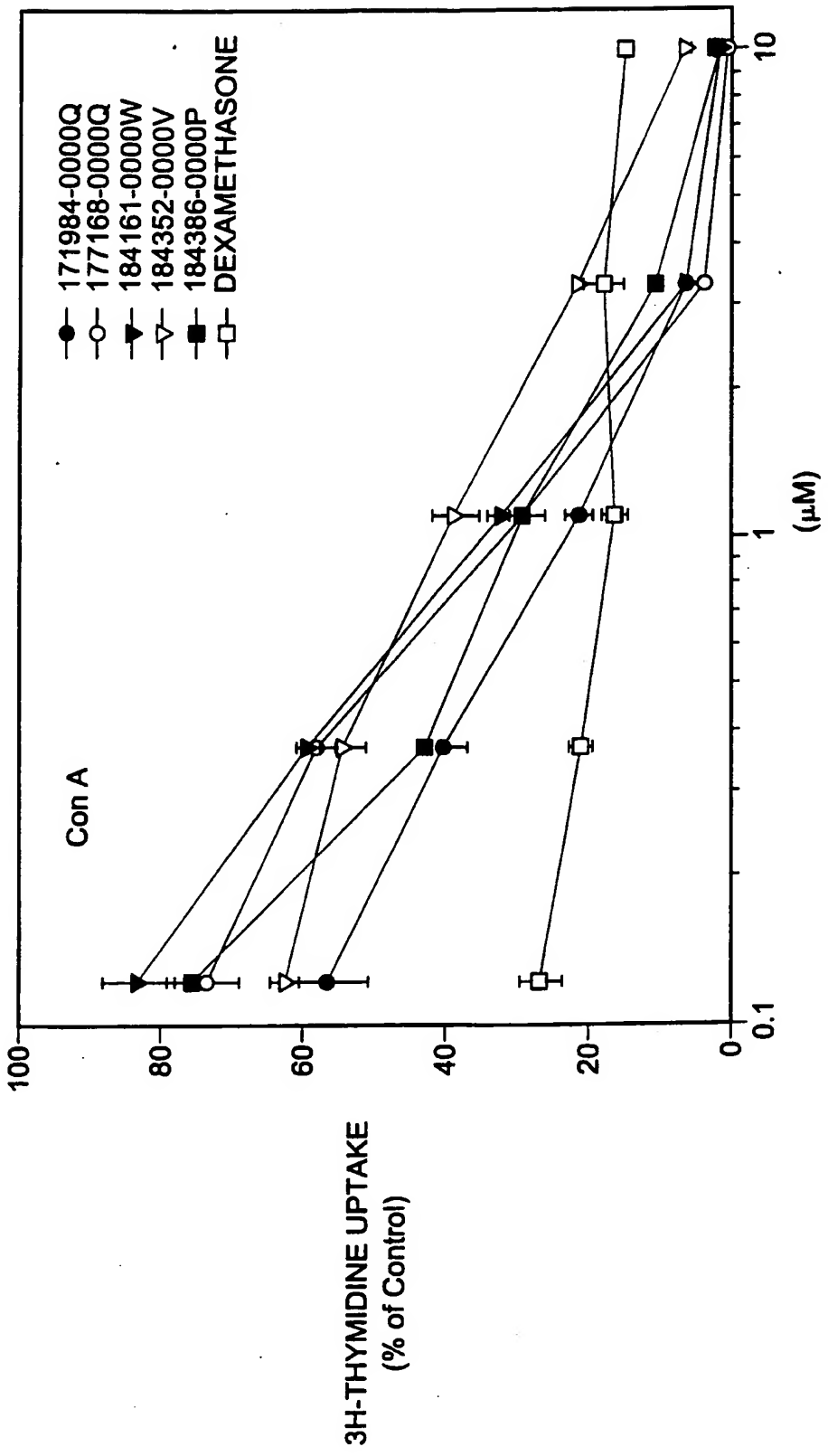


FIG. 12B MEK INHIBITORS SUPPRESS HUMAN T CELL PROLIFERATION

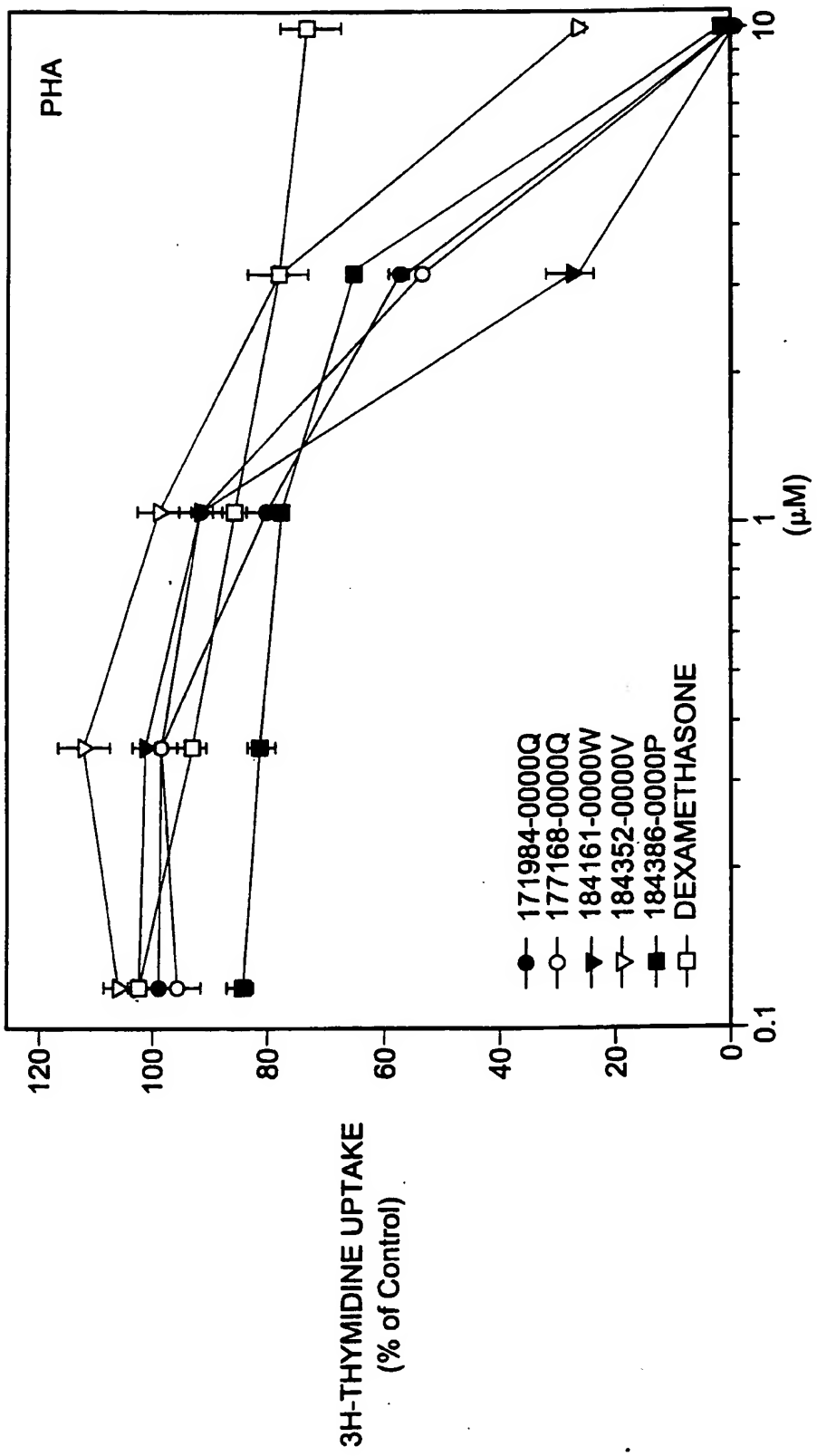
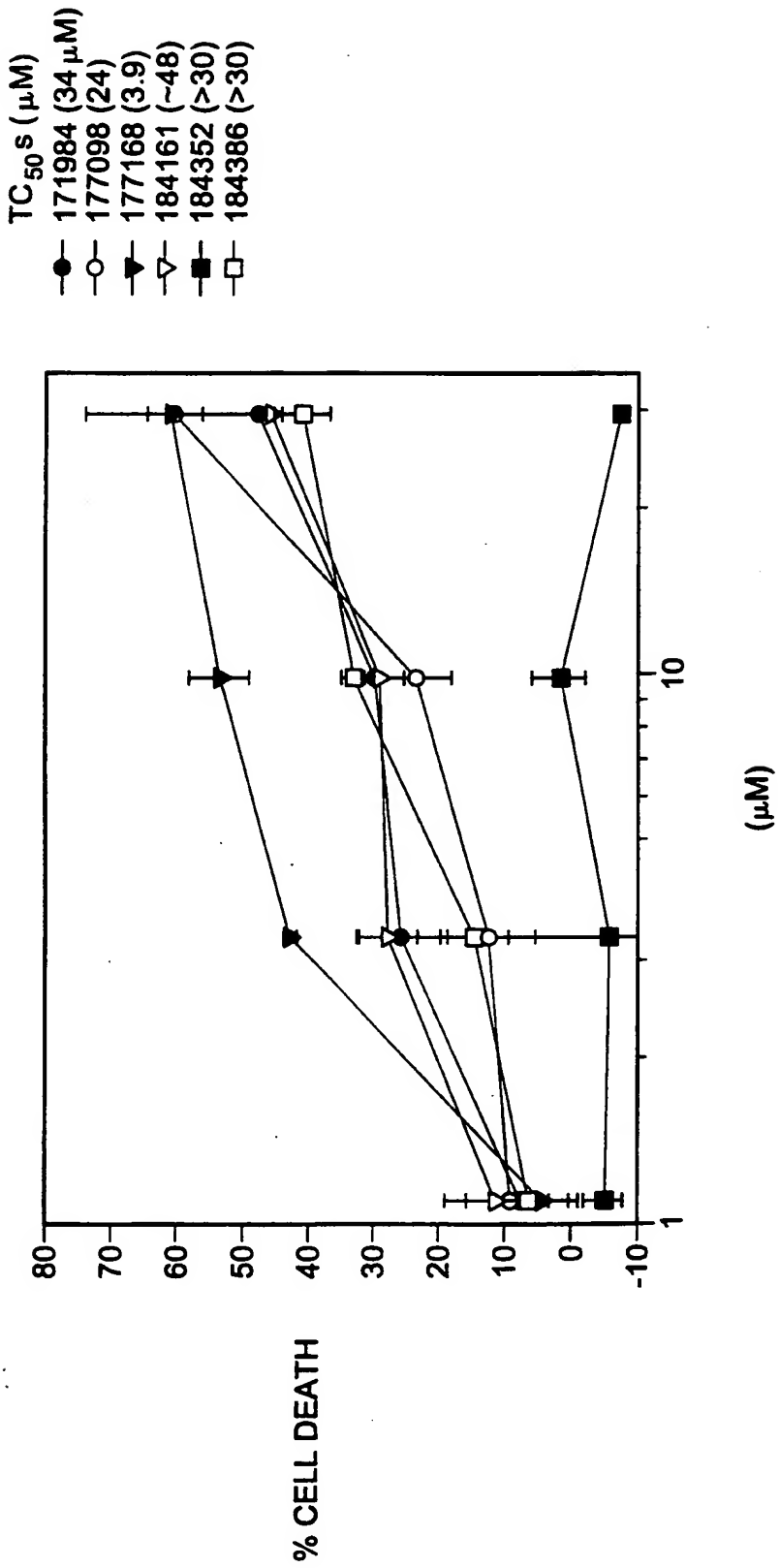


FIG. 13 MEK INHIBITORS, MTT TEST



INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/29591

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K31/196 A61K31/166 A61K31/136 A61K31/41
A61K31/495 A61K31/4453 A61K31/40 A61K31/4465 A61K31/5375
A61K31/381 A61K31/341 A61K31/18 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 34792 A (GEN HOSPITAL CORP) 15 July 1999 (1999-07-15) abstract page 2, line 1 -page 3, line 2 page 4, line 7 - line 21 page 14, line 2 - line 6; claims	1-3
X	WO 96 31206 A (WARNER LAMBERT CO) 10 October 1996 (1996-10-10) abstract page 3, line 10 - line 28 page 17, line 10 page 29, line 9 - line 15; claims page 39, line 26	1-3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/29591

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 22985 A (WARNER LAMBERT CO) 1 August 1996 (1996-08-01) cited in the application the whole document	1-3
X	WO 96 01111 A (WILLIAMS JAMES W) 18 January 1996 (1996-01-18) the whole document	1,3
P,A	MANNA S K ET AL: "Immunosuppressive leflunomide metabolite (A77 1726) blocks TNF-dependent nuclear factor-kappa B activation and gene expression." JOURNAL OF IMMUNOLOGY, (1999 FEB 15) 162 (4) 2095-102. , XP000907249 page 2100, right-hand column, paragraph 1 figure 7	1,3
Y	EP 0 316 630 A (WARNER LAMBERT CO) 24 May 1989 (1989-05-24) abstract page 8, line 51 - line 52 claims; examples 14,19	1,3,8,11
Y	WO 98 37881 A (BRIDGES ALEXANDER JAMES ;WARNER LAMBERT CO (US)) 3 September 1998 (1998-09-03) cited in the application abstract; claims; examples	1,3,8,11
P,A	WO 99 01426 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) the whole document	1-15
P,A	WO 99 01421 A (DOHERTY ANNETTE MARIAN ;BARRETT STEPHEN DOUGLAS (US); BRIDGES ALEX) 14 January 1999 (1999-01-14) the whole document	1-15

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 29591

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 29591

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,3 relate to a compound defined by reference to its pharmacological property, namely "MEK inhibitor".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Furthermore, present claims 4 and 8 relate to an extremely large number of possible compounds, namely any esters, amides or prodrugs of the compounds of formulae I and II. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds structurally identified in claims 2,4-15 and to their pharmaceutically acceptable salts, with due regard to the general idea underlying the present invention.

Claims searched completely: 2,5-7,9-15
Claims searched incompletely: 1,3,4,8

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ional Application No
PCT/US 99/29591

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9934792	A	15-07-1999	AU	1951499	A	26-07-1999
WO 9631206	A	10-10-1996	AU	5259296	A	23-10-1996
WO 9622985	A	01-08-1996	US	5525625	A	11-06-1996
			AT	181913	T	15-07-1999
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			US	5688824	A	18-11-1997
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			AU	2909289	A	23-05-1989
			WO	8903818	A	05-05-1989
			ZA	8807696	A	27-06-1990
WO 9837881	A	03-09-1998	AU	5610398	A	18-09-1998
			ZA	9801578	A	02-09-1998
WO 9901426	A	14-01-1999	AU	8262798	A	25-01-1999
			EP	0993439	A	19-04-2000
			HR	980368	A	30-04-1999
			NO	996491	A	29-12-1999
			ZA	9805728	A	27-01-1999
WO 9901421	A	14-01-1999	AU	8262698	A	25-01-1999
			EP	0993437	A	19-04-2000
			HR	980369	A	30-04-1999
			ZA	9805726	A	27-01-1999